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Rigorous Clinical Trials in Real World Settings

Marianthi Markatou, PhD
Professor of Biostatistics
University at Buffalo

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Outline

- Introduction
- Design Considerations
- Implementation
- Data Collection, Management and Analysis
- Addressing COVID-19 impact
- Conclusions
- Acknowledgments

Introduction

- Patient-Centered HCV Care via Telemedicine for Individuals on Opiate Substitution Therapy: A Stepped Wedge Cluster Randomized Controlled Trial
  - Pragmatic clinical trial that is evaluating onsite telemedicine encounters for HCV treatment compared to usual care-offsite referral. The trial thus, has two arms, one that corresponds to usual care and a second that corresponds to telemedicine. It is designed as a non-blinded, noninferiority trial. The main endpoint is binary, SVR determination, a biological endpoint.
  - Trial is being conducted at 12 opioid treatment programs (OTPs) throughout New York State.
  - We will discuss design considerations as well as data collection, management and analysis issues related to the trial.

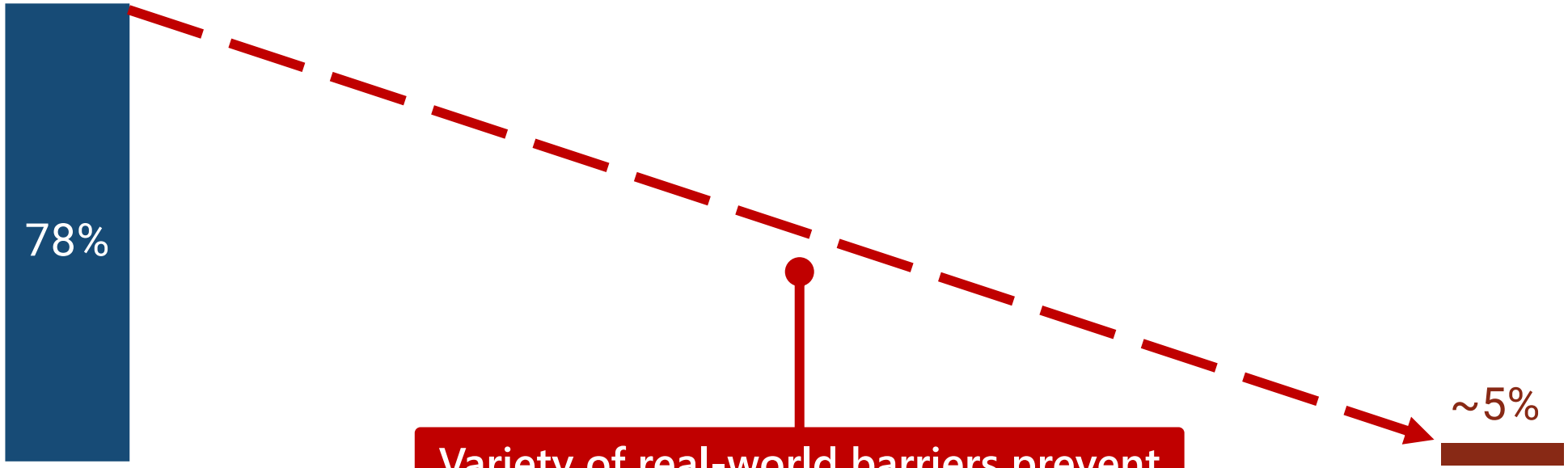
Hepatitis C Virus (HCV)

Virus that infects the liver
Spread through infected blood
Substance users & baby boomers
Untreated can lead to liver failure and liver cancer

Kills more Americans each year than HIV
+ 60 other infectious diseases combined

17,253 HCV-related deaths in 2017

A Difficult-to-Engage Population



78% of HCV+ patients at addiction centers are willing to get treated [1]

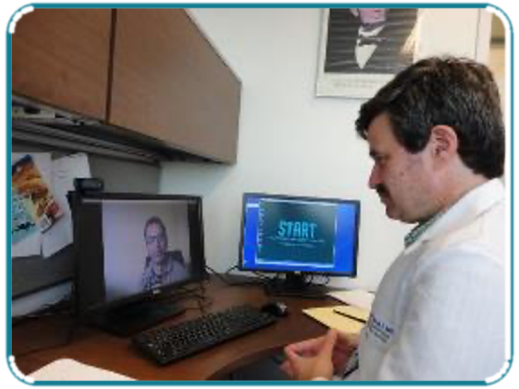
Variety of real-world barriers prevent HCV treatment access

- Lack of knowledge about HCV
- Lack of stable employment
- Unpaid time off work
- Competing priorities
- Limited or no insurance
- Stigma associated with substance use

Only ~5% of HCV+ patients with addiction get treatment

Reference: Zeremski M, Dimova RB, Zavala R, et al. Hepatitis C virus-related knowledge and willingness to receive treatment among patients on methadone maintenance. *J Addict Med*. 2014;8(4):249-257. doi:10.1097/ADM.0000000000000041

Patient-Centered Integrated HCV Treatment Model



Using patient-centered telemedicine, we integrate HCV care in the familiar and comfortable setting of substance use treatment

Opioid Treatment Program

- Up to 70% of patients have HCV
- But most programs lack on-site HCV screening and treatment

HCV Medication Revolution

- 95% efficacy
- 2-3 months of treatment
- All oral medications

Patient-Centered Integrated HCV Treatment Model

- Standard Internet Access
- Integrated care
- Remote Patient Engagement

HCV Treatment Model

Patient evaluations with HCV provider via video conference

Patient screened for HCV at opioid treatment program

HCV +

Patient-Centered Integrated HCV Treatment Model

HCV medication dispensed with patients existing methadone dose

Repeat until cured

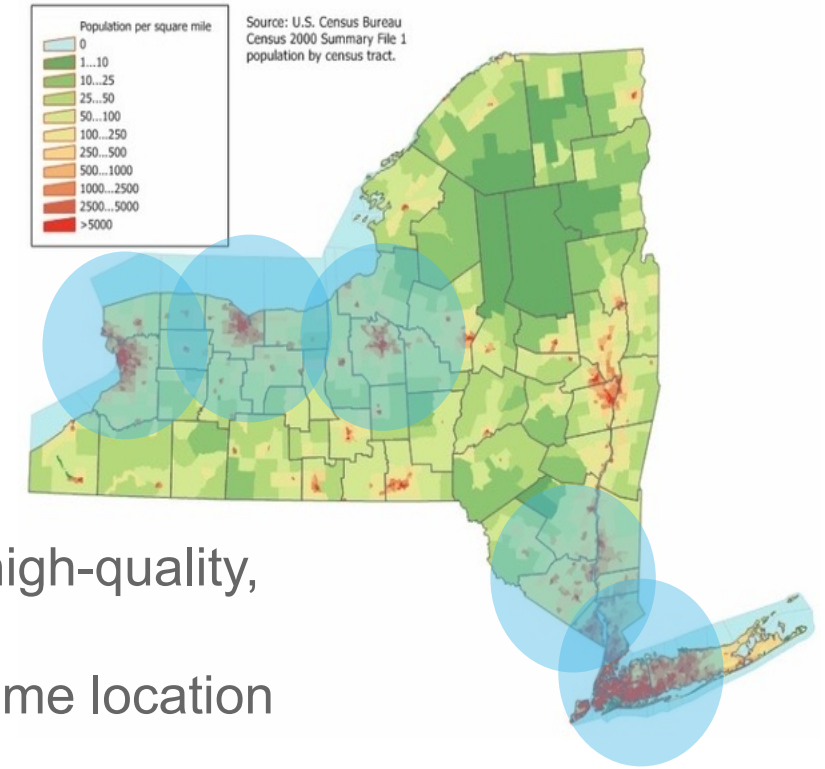
Patient and NP/PA at opioid treatment program

Our model results in:

- Trust between patient and provider
- Patients develop healthcare ownership
- Expanded sense of self and purpose
- Willingness to engage in greater care

Statewide Telemedicine Network

- Patient-Centered Outcomes Research Institute (PCORI) funded a study to integrate HCV treatment into OTPs via telemedicine
- Project recruitment: March 2017-Feb 2020
  - >600 patients enrolled
- 12 sites across NYS, covering most metropolitan areas (6 upstate, 6 in NYC)
- In our case:
  - Telemedicine:
    - Removes time and place as obstacles from delivery of high-quality, cost-effective healthcare
    - Permits providers to treat patients statewide from the same location



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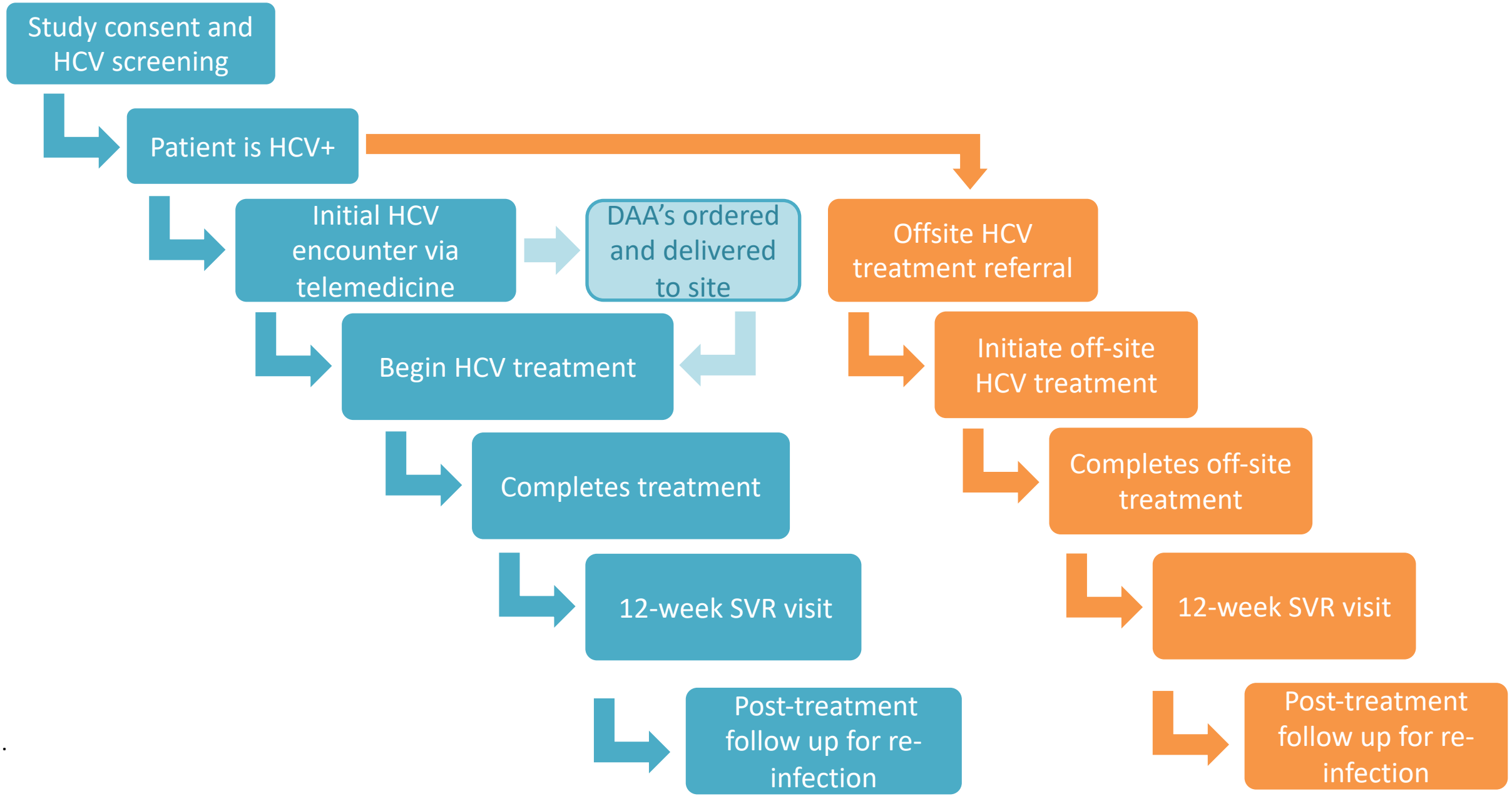
START
TREATMENT & RECOVERY CENTERS
The right way to treat people.

Mount Sinai
Beth Israel


Study consent and HCV screening
Patient is HCV+
Initial HCV encounter via telemedicine
DAA's ordered and delivered to site
Offsite HCV treatment referral
Begin HCV treatment
Initiate off-site HCV treatment
Completes treatment
Completes off-site treatment
12-week SVR visit
12-week SVR visit
Post-treatment follow up for re-infection
Post-treatment follow up for re-infection

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DESIGN CONSIDERATIONS

Clustered Randomized Trials (CRT)

- CRT are distinguished by the fact that the study participants are NOT randomized individually but are randomized in groups.
- Clustered designs are chosen for a variety of reasons. For example:
  - Intervention can only be administered on a community scale;
  - To minimize contamination;
  - Logistic, financial, or clinical concerns.

Stepped Wedge Design Trials (SWT)

- SWT are a specific type of clustered randomized trials. A SWD is a type of cross-over design in which:
  - Different clusters cross over (switch treatments) at different time points;
  - The clusters switch over in one direction only-from control to intervention.

Cluster Switching in SWT

- The first time point usually corresponds to a baseline measurement where none of the clusters receives the intervention of interest.
- At subsequent time points, clusters initiate the intervention of interest and the response to the intervention is measured.
- More than one cluster may start the intervention at a time point, but the time at which a cluster begins the intervention is randomized.

Stepped Wedge Cluster Randomized Control Trials

- Question: What are the primary reasons for selecting a SWD?

- Before answering this question, it may be useful to look at two types or research studies that use SWDs, exploratory and pragmatic.

Exploratory versus Pragmatic Research

- Exploratory research
  - The intervention is primarily implemented to study its effects;
  - Decisions of whether to further roll out the intervention are made after research is completed;
  - A SWD is considered if resources are insufficient to offer the intervention to all intervention clusters simultaneously.
- Pragmatic research
  - The intervention is primarily offered in order for it to exert its expected benefits;
  - Research insights are a secondary gain;
  - Decisions about where and when the intervention is to be delivered will be influenced by practical concerns;
  - Phased introduction may be planned for logistical reasons.

SWD Considerations

- Hargreaves et al (2015) suggest five questions to consider before one decides to use a SWD for use in a RCT.

- One of these questions relates to why a SWD trial is planned. In other words, what are the reasons for using a SWT?

Reasons for selecting SWD

- Primary reasons for selecting a SWD relate to logistical and ethical considerations.
  - However, phase implementation brings its own challenges. For example, it can
  - 1) require repeated training activities;
  - 2) Sustained engagement with the clusters in the control arm to avoid drop out;
  - 3) Increasing workload for intervention teams over time as more clusters initiate the intervention;
  - 4) May be difficult to ensure adherence to a randomly determined roll-out.

Reasons for Using a SWD

- Ethical equipoise – clear where it lies.
  - (Freedman, NEJM, 1987, 317, 141-5; Lilford, BMJ, 2003, 326, 980-1)
- Interest centers on effects of an intervention that is being rolled out, but about which there remains much to learn in a real-world setting, in a new context, or an outcome for which it has not previously been considered.
  - Such situations offer the most convincing justification for conducting a SWT.

SWTs Designs

- There are two types of designs associated with a SWCRCT.
  - Complete design: collects data at each and every step of the trial.
  - Incomplete design: at some steps, and for some clusters, data are not collected to contribute to the analysis. Often these designs involve only the incompleteness brought about by the implementation phase.

SWTs Designs-continued

- Cross-sectional: recruitment of new participants is happening at each step. Repeated measurements are not made on the same participants within a cluster – no serial correlation at the level of the individual unit.
- Longitudinal: repeated measurements are made on the same participant within a cluster.

Copas, AJ et al (2015), Trials, 16; 352.
Hemming, K, et al (2015), BMJ, 350: h391.

SWT: Telemedicine versus Usual Care for Delivering HCV Treatment

- Intervention: Telemedicine for delivering HCV treatment
- Control: Usual care –referral to an offsite specialist
- Population: Patients in Opioid Treatment Programs (OTP) dispersed throughout New York State.
- The trial was designed as a non-blinded stepped wedge clustered randomized controlled trial where the randomization unit was the clinic and not individual study participants.
- 12 OTPs constitute the clusters, and these were randomized in groups of four clinics.

SWT Design

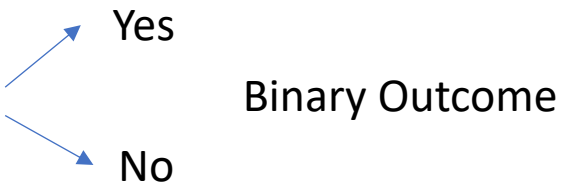
- Hence, our trial design can be depicted as follows:

Group		TIME (PERIOD)			
1	OTP	1 (0-9 mo.)	2 (9-18 mo.)	3 (18-27 mo.)	4 (27-36 mo.)
	1	UC	Tele	Tele	Tele
	2	UC	Tele	Tele	Tele
	3	UC	Tele	Tele	Tele
	4	UC	Tele	Tele	Tele
2	1	UC	UC	Tele	Tele
	2	UC	UC	Tele	Tele
	3	UC	UC	Tele	Tele
	4	UC	UC	Tele	Tele
3	1	UC	UC	UC	Tele
	2	UC	UC	UC	Tele
	3	UC	UC	UC	Tele
	4	UC	UC	UC	Tele

Abbreviations: UC- Usual Care; Tele-telemedicine; OTP-opioid treatment program; mo-months

Trial Design Considerations

- Outcome variable: sustained virological response (SVR)



- Thus, there are 3 steps, 4 time periods and 12 clusters in total, with 4 clusters within each group.
- UC is an active control, and clusters were randomized into the above 3 groups.

Randomization

- In cluster randomized trials, randomization increases internal study validity.
- It removes the possibility for systematically biased allocation and increases transparency.
- The importance of randomization in a SWT is that the effects of time can be estimated from the data, and bias from secular trends that would otherwise arise can be controlled for, provided the trends are correctly specified in the model[1].

[1]Hargreaves JR et al (2015), Trials, 16; 359.

Covariate-constrained Randomization

- We used covariate-constrained randomization:
  - Reduces the set of all possible randomizations to a subset (in which the differences between the study arms have been minimized);
  - There are criteria for achieving “reasonable” baseline balance across the arms;
  - Randomizations which satisfy these criteria are “acceptable”;
  - Only one of these acceptable randomizations is finally chosen.

[1]Moulton LH (2004), Clinical Trials, 1; 297-305.
[2]Chaudhary, MA, Moulton, LH (2006) Computer Methods & Programs in Biomedicine, 83: 205-10

Advantages of Covariate-constrained Randomization

- Limits the risk of selection bias;
- Achieves excellent balance of baseline characteristics;
- Improves power calculations

Disadvantages/Requirements of Covariate-constrained Randomization

- Requires access to baseline data;
- It should be well-understood;
- Requires a sufficient number of clusters
- Requires additional statistical support
  - Randomization involves several steps;
- Allocation must occur after recruitment

Randomization covariates

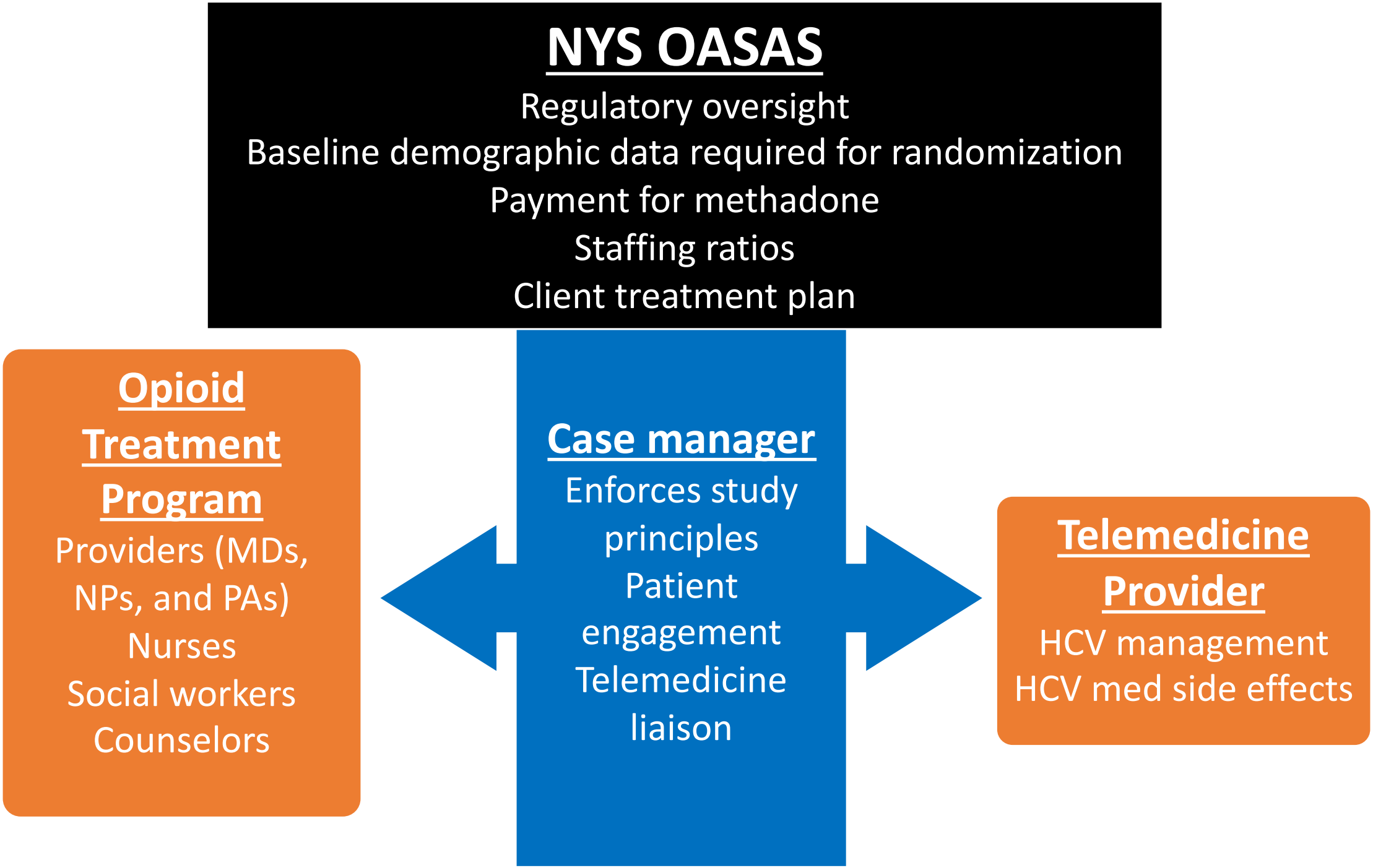
- In general, randomization covariates include both clinic variables and individual participant variables.
- In our case, the clinic variables were all comparable as the New York State Office of Addiction Services and Supports (OASAS) mandates those (i.e. staff ratios, attendance frequency, treatment plan, etc.)
- We use the covariates age, gender, ethnicity, race because
  - Age and race are surrogate variables to biologic confounders for SVR.
  - Gender and ethnicity were included to create balance between the two arms.
- Li et al have shown that constrained randomization improves the power of tests[1].

[1] Li, F, Turner, EL, Heagerty, PJ, et al (2017), Statistics in Medicine, 36: 3791-3806.

Implementation

Study implementation: Challenges and Solutions

- Up to 50% discontinuation in first three months in OTP
  - Inclusion criteria required six months in OTP.
- Medication cost
  - Study entry required active insurance or Medicaid support.
- Difficult-to-engage population
  - Linkage with OTP facilitates patient contact
- Issues of nonadherence
  - OTP dispensed HCV medications to increase adherence.


NYS OASAS
Regulatory oversight
Baseline demographic data required for randomization
Payment for methadone
Staffing ratios
Client treatment plan
Opioid Treatment Program
Providers (MDs, NPs, and PAs)
Nurses
Social workers
Counselors
Case manager
Enforces study principles
Patient engagement
Telemedicine liaison
Telemedicine Provider
HCV management
HCV med side effects

Site selection and interactions

- How to identify potential sites?
  - OASAS maintains comprehensive information on 126 methadone programs in NYS.
  - OASAS facilitated contact with potentially interested sites.
- Who facilitated participant recruitment and telemedicine encounters?
  - Study supported case manager handled all study-related procedures.
  - OTP staff supported study case manager
    - Clinical liaison present during telemedicine encounters.
    - Counselors-facilitated potential participant identification and subsequent contact
    - Nurses-responsible for HCV medication dispensing with methadone.
- How was engagement maintained over 5-year study?
  - Weekly meetings with sites to monitor progress.
  - Initial and annual HCV educational updates and sharing of study progress with each site.

Intervention implementation

- Introductory meetings to ensure adequate infrastructure.
  - Study purchased computers with camera and requisite specifications.
- Ensured adequate broadband-upload and download speeds.
- Education-Produced several educational videos
  - Testimonial video
  - HCV educational video
  - Telemedicine introductory video

Telemedicine Implementation Considerations

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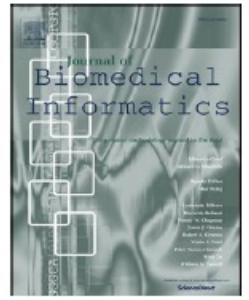
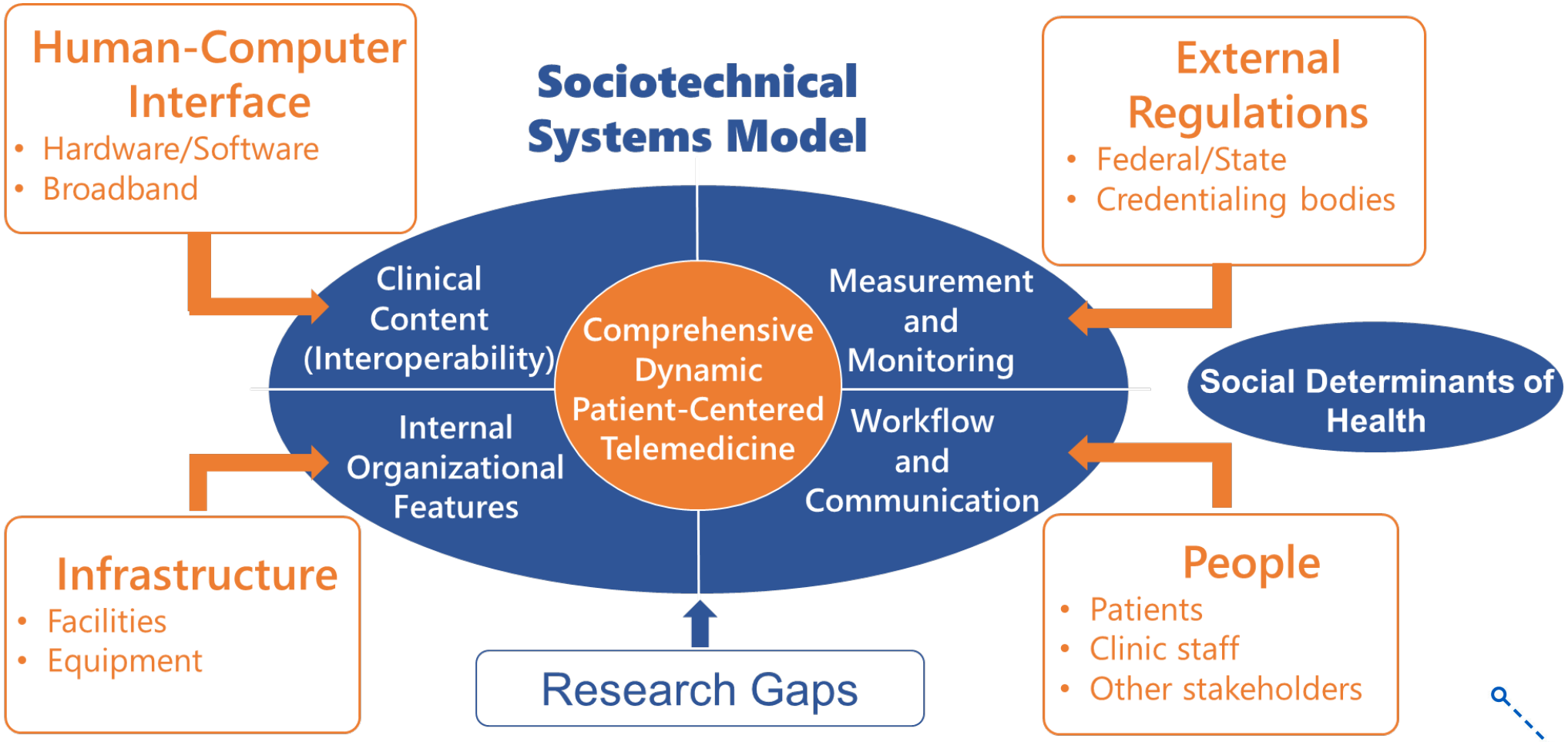


Special Communication

A framework for patient-centered telemedicine: Application and lessons learned from vulnerable populations

Andrew H. Talal [a], Elisavet M. Sofikitou [b], Urmo Jaanimägi [a], Marija Zeremski [c], Jonathan N. Tobin [c,d], Marianthi Markatou [b,*,1]

[a] *Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, United States*
[b] *Department of Biostatistics, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, United States*
[c] *Clinical Directors Network, Inc. (CDN), New York, NY, United States*
[d] *Center for Clinical and Translational Science, The Rockefeller University, New York, NY, United States*


Human-Computer Interface
• Hardware/Software
• Broadband
Sociotechnical Systems Model
External Regulations
• Federal/State
• Credentialing bodies
Clinical Content (Interoperability)
Measurement and Monitoring
Comprehensive Dynamic Patient-Centered Telemedicine
Social Determinants of Health
Internal Organizational Features
Workflow and Communication
Infrastructure
• Facilities
• Equipment
Research Gaps
People
• Patients
• Clinic staff
• Other stakeholders

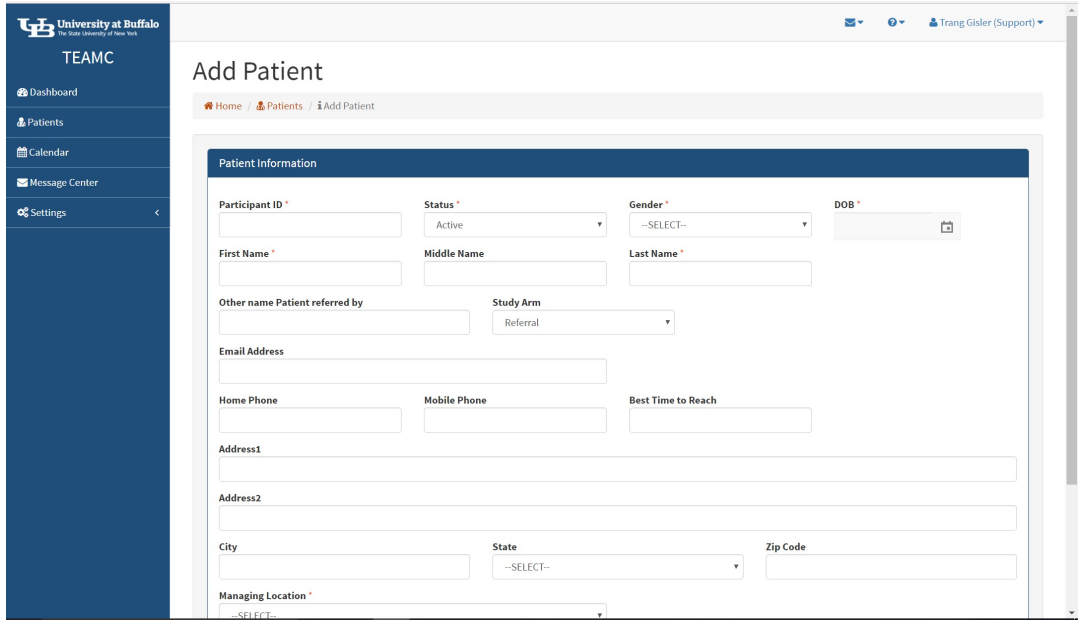
Lessons learned

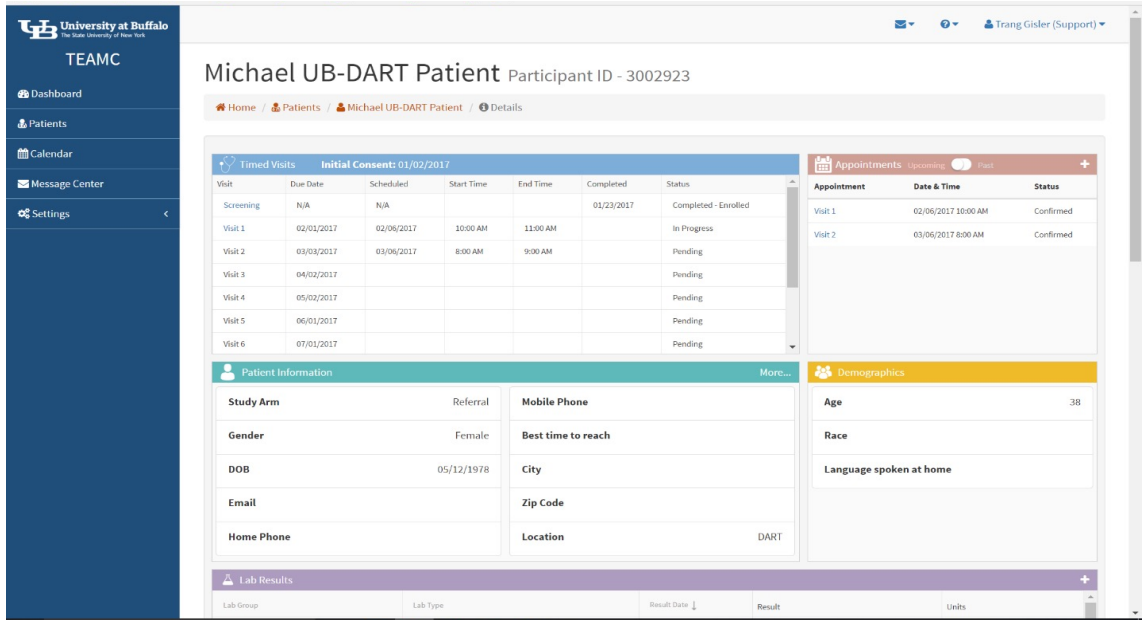
- Interoperability between all systems is critical for information flow
- Ensure detailed understanding of
  - Regulations (Federal, State, and organizational)
  - Licensure and credentialing requirements
  - Measurements of telemedicine quality; privacy and security
  - Evaluation and management codes for telemedicine
- Telemedicine for difficult-to-engage populations
  - Build trust and confidence with patients as partners
  - Minimize patient burden (e.g. simple systems, integrated appointments)
- Integrated telemedicine into OTPs leverages the trust patients have with OTP staff
  - Trust can be transferred from OTP staff to telemedicine provider

Data Collection, Management and Analysis

Data Capture System

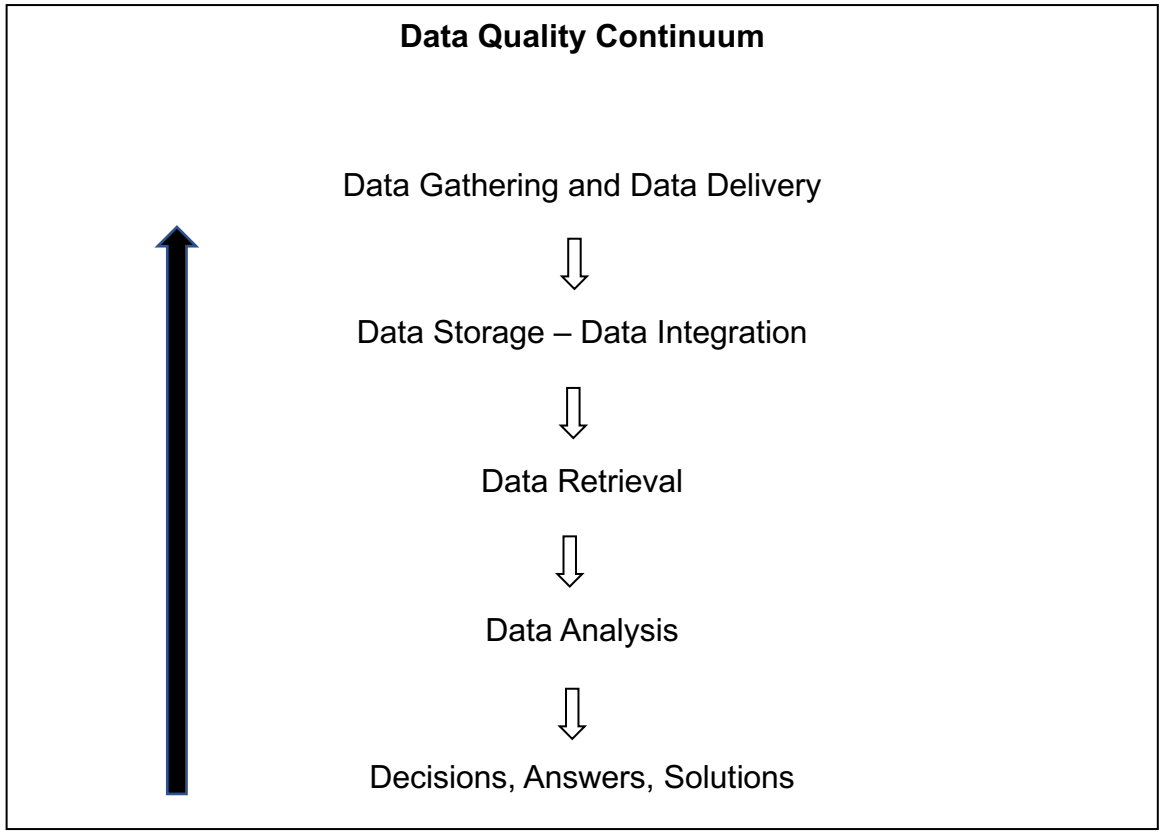
- We utilized an interactive web-based portal for study data collection.
  - Each site had permission-based access and credentials.
- Patient management system permitted study case managers to manage and capture all study related data.
- System permitted case managers to view patients' progress.





Data Quality

- Data quality is a continuum
  - From data gathering stage to analysis stage.

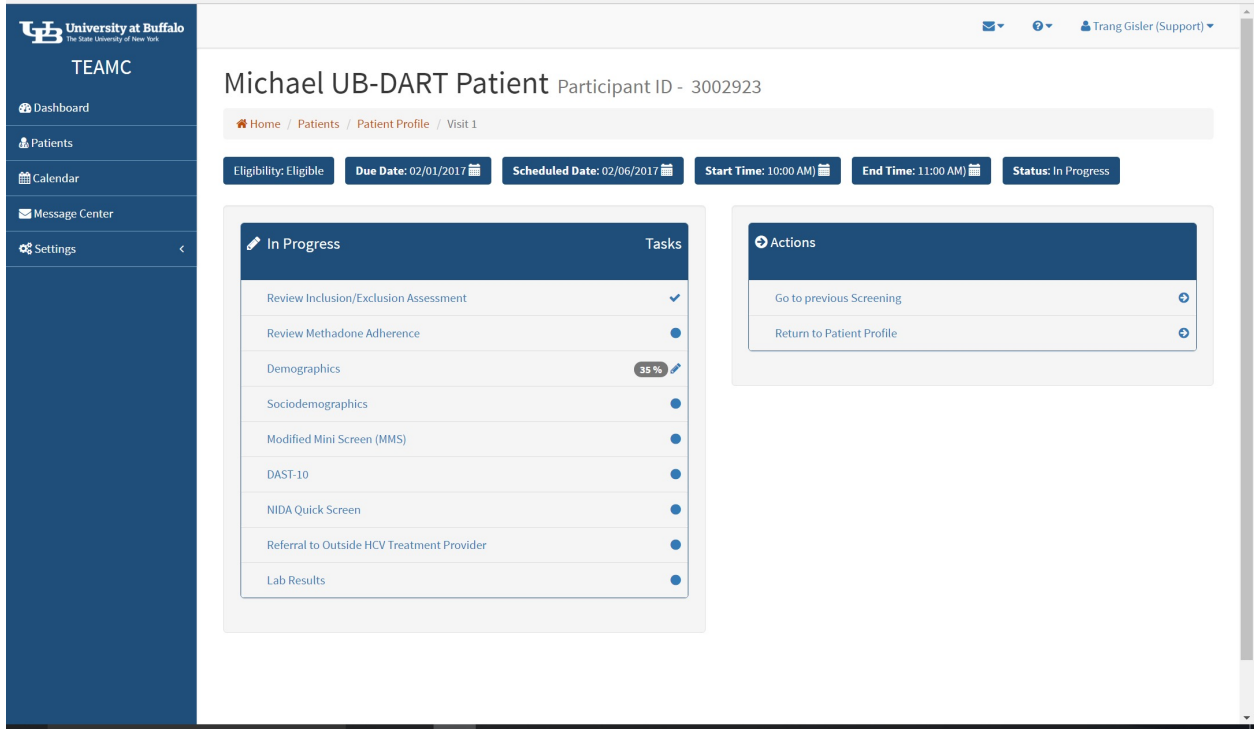


Missing Data and Missing Data Mechanisms

- **Definition**: Missing data are unrecorded data values that were intended to be collected, but they were not.
- Missing data can arise for a variety of reasons, including the inability or unwillingness of participants to meet appointments for evaluation. Missing data can seriously undermine the benefits of randomization and the scientific credibility of causal conclusions. Furthermore, the assumption that analysis methods can compensate for substantial missing data is not justified. There is no "foolproof" way to analyze data subject to substantial amounts of missing data since no method recovers the robustness and un-biasedness of estimates derived from randomized allocation to treatments.

Strategies to Limit Missing Data

- Data capture system
  - Demonstrates completeness of questionnaires collected at specific visits



Additional Strategies to Limit Missing Data

- Limit data quality issues
  - Mis-typed data
  - Incomplete data
  - Missing data
  - Duplicate entry data
  - Data out of range
  - Censored data
  - Truncated data
  - Default values
  - Outliers
- Drop-outs
  - Reported immediately

Additional Strategies to Limit Missing Data

- Each site has dedicated case manager/data steward
- All study personnel are trained on the importance of missing data
- Adherence to treatment schedule is monitored closely.
- Request to complete all surveys in person (modified during COVID)
- Case managers are responsible for **complete and accurate** data collection.
- Study participants informed at consent stage of need to complete surveys.
- Data collection monitored and reported consistently throughout trial.
- Remind participants frequently of study visits.
- Short follow up periods yield reductions in missing data.
- Educate participants on the importance of continued engagement.
- Provide non-monetary incentives-
- Keep participants' contact information up to date.
- If missing data are present, the Data Safety and Monitoring Board (DSMB) will be notified and the site needs to discuss with the DSMB strategies and schedules for alleviating this issue.
- Collect information on which subjects are at risk for dropping out and why.
- Whenever a participant discontinues some or all types of participation the following must be documented;
    - Reason for discontinuation;
    - Who decided the subject's discontinuation from the study;
    - Whether discontinuation involves some types or all types of participation.

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Practical, site-level strategies for handling missing data

- **If missing data are encountered, the following steps were taken:**
- Upon identification of missing data an email reporting 1) the occurrence of missing data; 2) the actions that are taken to resolve the issue; 3) the deadline by which the issue is expected to be resolved, was sent to the site case manager.
- The case manager investigated whether it is possible to retrieve the data. If data could not be retrieved the following steps were taken:
  - Collect auxiliary information that clearly presents the reasons for each missing data value. Each missing data value must be recorded separately with clear identification number and clearly stated reason(s) as to why this issue is present. This information guides the identification of the operating missing mechanism that is extremely important for carrying out a causal statistical analysis.
  - Each site reported the percentage of missing data for each subject on a weekly basis.
- Therefore, if there are circumstances that are absolutely unavoidable the upper limit of allowance for missing data is 2%-3% of the total amount of data collected in the trial. We aimed to minimize missing values.

Missing Data Mechanisms

- Missing Completely at Random (MCAR)
  - Missingness is unrelated to observed or unobserved data.
- Missing at Random (MAR)
  - The missing mechanism depends on the observed data, but conditionally on the observed data, the missing mechanism is unrelated to unobserved data.
- Missing Not at Random (MNAR)
  - Missing mechanism does not follow the above conditions (informative missingness)

Resources

- Li, T., Hutfless, S., Scharfstein, D.O. et.al (2014). Standards should be applied in the prevention and handling of missing data for patient-centered outcomes research: a systematic review and expert consensus. *Journal of Clinical Epidemiology,* 67, 15-32.
- Little, RJ, Cohen, ML., Dickersin, K. et.al. (2012). The design and contact of clinical trials to limit missing data. *Statistics in Medicine*, 31, 3433-3443.
- Little, RJ., D'Agostino, R., Cohen, ML., et.al. (2012). The prevention and treatment of missing data in clinical trials. *New England Journal of Medicine,* 367, 1355-1360.

Analysis Protocols

- Ideally, the analysis method for a SWT will result in:
  - An unbiased estimate of the intervention effect;
  - Appropriately reflect the level of uncertainty in the point estimate;
  - Be as statistically efficient as possible.

Cluster Randomized Trials Principles Can Guide SWT Analysis

- Since SWTs are types of CRTs, the principles of analysis for CRTs can be used to guide the analysis of SWTs.
- For example, data on individuals, or any other sub-cluster unit, are likely to be correlated with data from others in the same cluster.
- There is a rich literature on this issue because it arises in parallel CRTs as well.
  - See Hayes, RJ, Moulton, LH (2017). Cluster Randomized Trials, Second Edition, Chapman & Hall/CRC).

Additional Challenges in SWT Analysis

- Analysis of SWTs poses some additional challenges. Specifically, in SWTs, the intervention effect estimate is potentially confounded by secular changes in the outcome.
- Taking these issues into consideration, there are several ways to analyze data from SWTs. These are primarily individual-level analyses and adopt one of two broad approaches to address potential bias for secular trends.

Approaches to Analysis of SWT Data

- First approach (vertical analysis)
  - Compares outcomes associated with the control and intervention conditions within the periods between successive crossover points.
  - This approach implicitly takes into account secular trends by conditioning on time.
  - Observations corresponding to periods when all clusters are in the control or intervention condition do not contribute to the effect estimate. Parametric or semi-parametric models include conditional logistic regression or Cox regression.
  - Alternatively, we calculate the intervention effect size for each of several time intervals, such as, the periods between successive cross-over points.
  - We subsequently plot or summarize these data.

Advantages and Disadvantages of the First Approach

- Advantages
  - It preserves the randomization;
  - It avoids the need to specify time trends in the outcome
- Disadvantages
  - It is unclear how to acknowledge appropriately the clustering of participants over time within clusters.

Second Approach (horizontal analysis)

- This approach explicitly takes into account secular trends by producing an intervention effect adjusted for time trends which are also estimated.
- This method compares outcomes corresponding to the control and intervention conditions within the periods between successive cross-over points, as well as between these periods in the same clusters, and has maximum efficiency.

Second Approach

- For details on this approach see
  - Hussey, MA, Hughes, JP (2007). Contemporary Clinical Trials, 28, 182-91.
  - Baio, G, Copas, A, Ambler G, et al (2015), Trials 16: 354.
- This comparison includes, along with the vertical comparison, a controlled before-after comparison, that is <u>not,</u> strictly viewed, a randomized comparison. The validity of this *requires that the time trend of the outcome be accounted for in each cluster*.

Secular Trends

- Secular trends may arise because of:
  - 1) Changes in the level of the outcome in the population;
  - 2) From changes in the constituents of the sample in the trial (e.g. from attrition in a closed cohort).

- Time trends are incorporated usually in the model as fixed effects, often as factors reflecting the periods between crossover points.
- Assumption: the trend is the same in all clusters (however, this assumption may not apply in certain situations).

Modeling

- Individual-level models can gain efficiency and appropriately reflect the level of uncertainty in the point estimate.
- The clustering in the data is reflected either via incorporation of a random effect in a mixed-effects model (or GLME model) or via use of generalized estimating equations (GEE) with a working correlation matrix.
- Multiple levels of clustering can also be taken into account with these methods.
- Adjustments for individual and cluster-level covariates can also be made with these methods.
- Correct specification of the model and time effects is important to avoid bias in the intervention effect.

Addressing COVID-19 Impact

Effects of COVID-19

- In March 2020, the novel coronavirus 2019 (COVID-19) pandemic necessitated discontinuation or severe restriction of all in-person encounters. These restrictions impacted in different ways and degrees the clinical, operational, and data collection activities of the study.
- Study recruitment was completed immediately before the restrictions imposed by the pandemic-therefore, there was no impact on study recruitment.

Effects of COVID-19

- Data collection: Was partially impacted in that
  - 1) Some data had to be collected over the phone;
  - 2) The likelihood of missing values increased.
- Clinical aspects were impacted. Specifically, we observed:
  - 1) Delays in HCV treatment initiation;
  - 2) Decreased frequency of HCV medication pick-up;
  - 3) Delays in determining the outcome of SVR.

Effects of COVID-19

- Operational aspects that were impacted are as follows:
  - Scheduling and coordination of blood collection needed for the study was extremely challenging.
    - Study participants had concerns of COVID acquisition if they appeared in healthcare settings, such as laboratories for phlebotomy.
  - Depending upon the site, in-person visits were either restricted or suspended.
    - Increased reliance on telephone visits.
    - When in-person visits were permitted, tight scheduling replaced unscheduled walk in OTP visits.
  - Childcare issues were expanded due to daycare and school closures.

Procedures Implemented to Increase Study Adherence

- Increase in take-home medications.
- Case managers maintained frequent contact (electronic or via phone) with study participants – to avoid participant drop out.
- Healthcare workers made home visits wearing PPE.
- Personalized approaches to obtain blood draws for SVR determination
  - Minimize missing values.
- Transform the facility to obtain proper social distancing.

Assessing and Addressing the Impact of COVID-19 Analytically

- Wiens, B & Lipkovich, I. (2020), Statistics in Biopharmaceutical Research, 12(4), 443-50 discusses the impact of major COVID-19 created events on ongoing non-inferiority trials, with an emphasis on missing data and its impact on the analysis.
- Typical situations where missing data are caused by COVID-19 originate from:
  - A site may be unable to fulfill the obligations under the protocol
  - Site closures – participants and personnel unable to travel to the study site.
- In our study, we collect the reasons for missing values. We then use these to classify the missing mechanism of the missing observation and then use appropriate statistical techniques to account for missing values in the analysis.

Conclusions

- Leveraging regulations and infrastructure designed to deliver clinical services can be utilized to conduct research
- The SWD can be highly effective for pragmatic clinical trials when considered and implemented appropriately.
- Team is extremely important for the conduct of pragmatic clinical trials.

Patient-Centered HCV Care via Telemedicine for Individuals on Opiate Substitution Therapy: A Stepped Wedge Cluster Randomized Controlled Trial

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SUNY/University at Buffalo
Andrew H Talal, MD, MPH (PI)
Elisavet Sofikitou, Ph.D. (Biostat. Res. Assoc.)
Yuxin Ding, Ph.D. (Biostat.)
Kejia Wang, MA (Biostat., student assistant)
Suzanne S. Dickerson, DNS (Co-I)
Urmo Jaanimagi, MA, MS (Project Director)
Arpan Dharia, MD (Case Manager)
Barbara Bauer, BA (Case Manager)

Start Treatment & Recovery Centers
Lawrence S. Brown, MD, MPH (co-PI)
Anthony McLeod (Case Manager)
Jordan Bailey, MBS (Case Manager)

Clinical Directors Network, Inc.(CDN)
Jonathan N. Tobin, PhD (co-PI)
Marija Zeremski, PhD (co-PI/Project Director)
Karen Morton (Case Manager)

Mount Sinai Beth Israel
Don C. Des Jarlais, PhD (co-PI)
Ponni V. Perumalswami, MD (co-PI)
Amreen Dinani, MD (co-PI)
Nancy Nugent, (Senior Research Assoc)
Saliyah George, MPH (Case Manager)

University of Rochester
Marc T. Swogger, PhD (co-PI)
Kathleen Davis, NP (Nurse practitioner)

University at Buffalo
The State University of New York

CDN
CLINICAL•DIRECTORS•NETWORK

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Q&A Session