Trials

LETTER

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Irregular assessment times in pragmatic randomized clinical trials

Andrea Apter[1], Frances K. Barg[2], Sanjib Basu[3], Alex Federman[4], Winifred J. Hamilton[5], Jerry A. Krishnan[6], Tianjing Li[7], Russell Localio[8], Christine Pindle[9], Daniel O. Scharfstein[10*], Justin D. Smith[11] and Kaharu Sumino[12]

Abstract

Deviation from protocolized assessment times is commonplace in pragmatic randomized clinical trials. Working with a stakeholder advisory board for a Patient-Centered Outcomes Research Institute®-funded project on statistical methods for handling potential biases introduced by irregular assessment times, we identified reasons for off-schedule or missed assessments. We used the Consolidated Framework for Implementation Research 2.0 to organize our findings. We conjectured that timely completion of outcome assessments is a function of multiple determinants, only some related to participants' health status. We identified potential determinants that can be modified during the protocol design stage and can be reassessed and mitigated during trial implementation stage. Research to more formally evaluate our findings is warranted as well as studies to evaluate multi-level strategies that reduce off-schedule or missed assessments.

Keyword Implementation science, Determinants of off-schedule or missed assessments, Stakeholder perspectives

*Correspondence:
Daniel O. Scharfstein
daniel.scharfstein@hsc.utah.edu
[1] Department of Allergy & Immunology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[2] Department of Family Medicine and Community Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[3] Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois Chicago, Chicago, IL, USA
[4] Division of General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[5] Departments of Family & Community Medicine, Medicine, and Neurosurgery, Baylor College of Medicine, Houston, TX, USA
[6] Breathe Chicago Center, Division of Pulmonary, Critical Care, Sleep, and Allergy, University of Illinois Chicago, Chicago, IL, USA
[7] Department of Ophthalmology, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[8] Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[9] Certified Nursing Assistant, Community Advisory Board HAP3 Study, University of Pennsylvania, Philadelphia, PA, USA
[10] Department of Population Health Sciences, Division of Biostatistics, School of Medicine, The University of Utah, Spencer Fox Eccles, Salt Lake City, UT, USA
[11] Department of Population Health Sciences, Division of Health System Innovation and Research, Spencer Fox Eccles School of Medicineat, The University of Utah, Salt Lake City, UT, USA
[12] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, USA

Main text

Despite pre-specification of outcome assessment times in pragmatic randomized trials, participant deviation from these times is commonplace. A key analytic concern is whether there are factors linked to the outcomes of interest that are driving these deviations. Off-schedule or completely missed assessments may be related to participants' health status—such as poor health or feeling well enough to engage in other activities (e.g., work, school, caregiving). Differences between the health status at the observed assessment times and the health status at the pre-specified assessment times can result in overestimation or underestimation of the harms or benefits of study interventions [1].

The Patient-Centered Outcomes Research Institute® (PCORI®), a nonprofit organization established by the Affordable Care Act in 2010 in the United States, funded our group to develop and disseminate a statistical methodology to account for irregular (i.e., off-schedule or missed) assessment times in pragmatic randomized clinical trials. PCORI® values pragmatic randomized trials because they produce practical, actional evidence that can directly impact patient care and improve health outcomes in real-word settings. Irregular assessment times in these trials present a significant challenge for trialists in estimating unbiased treatment effects.

Our project focused on trials evaluating interventions to improve care for patients with chronic diseases and limited socioeconomic resources. Members of the investigator group (authors AA and JK) conducted four pragmatic randomized clinical trials: two enrolled adults with asthma (ARC [2]—NCT02086565 and HAP2 [3]—NCT01972308), one enrolled children presenting with uncontrolled asthma to emergency departments (CHICAGO Plan [4]—NCT02319967), and the fourth enrolled adults hospitalized for heart failure, myocardial infarction, pneumonia, COPD, or sickle cell disease (PArTNER [5]—NCT02114515). All four pragmatic trials were designed to test interventions under real-world conditions and experienced substantial missingness and irregularity of assessment times (see Table 1 and Fig. 1); in ARC and HAP2, primary outcomes were assessed in clinic or by

Table 1 Missing and out-of-window assessments, by treatment group, for four studies

Study	Treatment	Sample Size	Assessment 1		Assessment 2		Assessment 3		Assessment 4	
			Missing	Out of Window	Missing	Out of Window	Missing	Out of Window	Missing	Out of Window
ARC	PT	150	4 (3%)	95 (63%)	13 (9%)	107 (71%)	37 (25%)	88 (59%)	71 (47%)	34 (23%)
	PT+HV	151	10 (7%)	84 (56%)	18 (12%)	110 (73%)	47 (31%)	83 (55%)	74 (49%)	50 (33%)
HAP2	Usual Care	156	7 (5%)	73 (47%)	21 (13%)	112 (72%)	40 (26%)	105 (67%)	9 (6%)	141 (90%)
	Patient Advocate	156	10 (6%)	74 (47%)	18 (12%)	102 (65%)	34 (22%)	113 (72%)	9 (6%)	140 (90%)
PArTNER	Usual Care	511	105 (21%)	60 (12%)	137 (27%)	18 (4%)				
	Intervention	518	127 (25%)	67 (13%)	155 (30%)	27 (5%)				
CHICAGO Plan	Usual Care	126	28 (22%)	19 (15%)	38 (30%)	14 (11%)	48 (38%)	12 (10%)		
	CAPE	126	23 (18%)	19 (15%)	20 (23%)	7 (6%)	44 (35%)	13 (10%)		
	CAPE+Home	121	26 (21%)	13 (11%)	38 (31%)	12 (10%)	45 (37%)	11 (10%)		

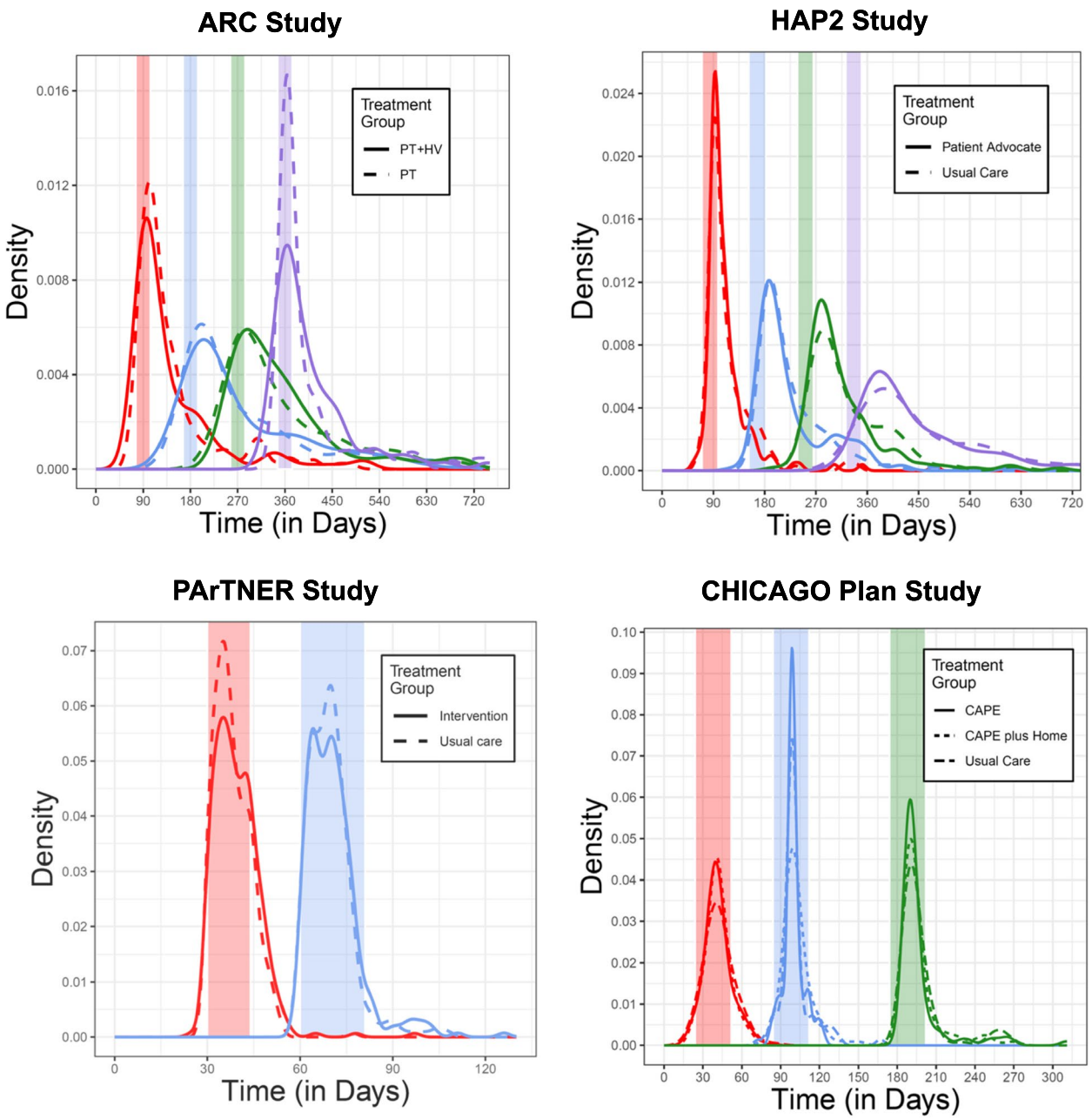
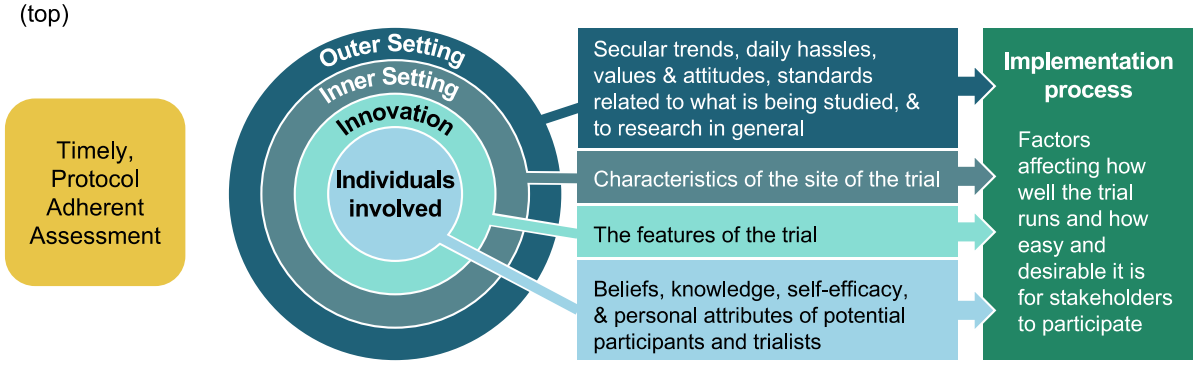


Fig. 1 Distribution of actual vs. targeted assessment times for four studies. Treatment-specific distributions of the actual time of first (red), second (blue), third (green), and fourth (purple) scheduled assessments. Shaded regions reflect assessment windows

phone, depending on the preference of the participant, and in CHICAGO PLAN and PArTNER, primary outcomes were assessed by phone.

To provide first-hand insights into the problem, our project is informed by a diverse Stakeholder Advisory Board (SAB), consisting of two individuals from affected populations (i.e., people with asthma or other conditions relevant to the study protocol), clinicians, clinical trialists, implementation scientists, a qualitative researcher, and biostatisticians. Importantly, the researchers on the SAB have diverse expertise extending beyond the type of behavioral trials highlighted above, including substantial experience with trials outside the United States. The initial SAB activities were devoted to understanding, from the stakeholders' perspective, what might cause patients to postpone or miss a pre-specified assessment. In a meeting of the entire SAB, members generated a list of reasons for off-schedule or missed assessments. The

(top)



(bottom)

CFIR DOMAIN AND CONSTRUCTS	EXAMPLES
Outer setting	Covid-19 Weather (snowstorms, hurricanes) ★Norms, values, trust in science, trust in the health system Political environment Performance pressures (scientific validity as a professional norm)
Inner setting	★Burden to the clinical environment in which the intervention is taking place (e.g., staffing, rooms) ★ Study activities take place during routine clinical care, at home, or other locations convenient to the participant ★ Study staff make the participant feel valued ★ Study assessment schedule dictated by trialists' needs
Innovation	★ Design of the trial ★ Demands of the trial ★ Flexibility with the needs of the participant/rigidity of the window of assessment
Individuals involved	Innovation recipients (study participants) ★Hassles (parking, travel, location of assessment) ★Resonates with their own health situation, direct ★ Appreciate hands-on personal attention, feels valued ★Health situation perceived to be serious ★Other responsibilities (work, caregiving) ★Trust/distrust ★Want to know why study activities are needed (help them become partners, improves respect)
	Innovation deliverers (trialists/research team) Pressure to maintain rigor Pressure to recruit Pressure to maintain validity ★ Communication skills –clear rationale about the trial protocol (e.g., monthly visits on time) and methods (e.g. randomization)
Implementation process	★ Study procedures are arranged around the participant's preferences (as protocol permits) ★ Study staff consider the participant's unique situation ★ Compensation conveys respect for participant's time and involvement ★ Return of individual results to participants in a way that provides "value" to study participants in a timely way

Fig. 2 (Top) CFIR 2.0 domains to consider to optimize protocol adherence in a clinical trial. (Bottom) Examples of constructs within each CFIR 2.0 domain that affect protocol adherence in a clinical trials; stars indicate modifiable factors

list reflected the diverse perspectives and experiences that each member brought to the elicitation process. Authors FKB and JDS created a coding tree to sort the reasons into discrete categories. The coding tree included codes for the five key domains (outer setting, inner setting, innovativeness of the trial, individuals involved, and implementation process) in the Consolidated Framework for Implementation Research 2.0 (CFIR2.0) [6] and subcodes describing who or what causes off-schedule or missed assessments in each of those domains. CFIR2.0 was selected because it provides a systematic approach for understanding the multiple domains (determinants) of study implementation, including various features of the study (e.g., pre-specified data collection schedule).

Figure 2 (top) displays the relationship among the domains, and Fig. 2 (bottom) provides examples of key constructs within each of the CFIR2.0 domains. Our insight from this process is that the timely completion of outcome assessments is a function of multiple determinants, only some of which are related to participants' health status. Importantly, we identified determinants of irregular assessment times that can be modified during the protocol design stage (e.g., developing study protocols that are feasible for both participants and study implementers). At the protocol implementation stage, investigators can then reassess barriers and enact flexible mitigation plans to reduce the risk of irregular assessments (e.g., collection of outcomes via home visits, rather than depending on participant travel to clinics or study sites).

Our preliminary observations stem from four localized behavioral trials conducted by researchers at two universities as well as the extensive experience of our SAB. We conjecture that our observations are generalizable to other pragmatic trials, including those that are geographically diverse, non-US-based and involve pharmaceutical treatments. Research to more formally evaluate this conjecture is warranted as well as studies to evaluate multi-level (e.g., participant- and study procedure-level) strategies that reduce off-schedule or missed assessments.

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Data availability
All data and materials are in the letter.

Declarations

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N/A.

Consent for publication
All authors have consented to publication.

Competing interests
The authors declare no competing interests.

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