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Where to Next for Optimizing Adherence in Large-scale Trials of CPAP?

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Abstract

Large-scale randomized trials of positive airway pressure (PAP) efficacy have been largely negative yet PAP adherence was notably sub-optimal across the trials. To address this limitation, evidence-based PAP adherence protocols embedded within the larger trial protocol are recommended. The complexity of such protocols will be dependent on adequacy of resources, including funding and inclusion of behavioral scientist experts on the scientific team, and trial-specific considerations (e.g., target population) and methods. Recommendations for optimizing PAP adherence in large-scale trials are set forth that address rigor and reproducibility.

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Comments

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Optimizing Adherence in Trials

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Keywords (MeSH): Obstructive Sleep Apnea; Continuous Positive Airway Pressure; Patient Compliance; Health Behavior; Telemedicine; Health Education; Controlled Clinical Trial; Behavioral Economics

Key Points:

- Large-scale, randomized trials to evaluate efficacy of positive airway pressure (PAP) for improving patient-reported outcomes and clinical endpoints associated with obstructive sleep apnea (OSA) including cardiovascular and metabolic disease have been largely negative.

- Several design-related criticisms have plagued the large-scale PAP trials with a common focus on PAP non-adherence among trial participants.

- Advancing large-scale PAP trial methods to optimize PAP adherence is crucial if the field is to be successful in generating valid knowledge of the causal effect of OSA on comorbid outcomes.

- "Best trial practices" that focus on optimizing PAP adherence in large-scale trials are needed.

Synopsis:

Large-scale randomized trials of positive airway pressure (PAP) efficacy have been largely negative yet PAP adherence was notably sub-optimal across the trials. To address this limitation, evidence-based PAP adherence protocols embedded within the larger trial protocol are recommended. The complexity of such protocols will be dependent on adequacy of resources, including funding and inclusion of behavioral scientist experts on the scientific team, and trial-specific considerations (e.g., target population) and methods. Recommendations for optimizing PAP adherence in large-scale trials are set forth that address rigor and reproducibility.

Where to Next for Optimizing Adherence in Large-scale Trials of PAP?

Introduction

Clinical trials are defined as experiments in humans designed to evaluate the effects of specific treatment(s), or exposure condition(s), by reducing random error and bias.[5] Effects or outcomes evaluated in clinical trials commonly include safety, dosing, efficacy and effectiveness. Phase III trials that evaluate efficacy and/or effectiveness of a treatment compared to a standard, alternative or placebo are often designed as large-scale to ensure adequate statistical power and potentiate generalizability to the defined target population.[5] For the purpose of this paper, large-scale trial characteristics include the following: 1) multi-site; 2) total sample size greater than 300 participants; and 3) a primary outcome evaluation period greater than or equal to three months.

In the field of sleep medicine, large-scale trials that meet the above criteria and examined the effects of positive airway pressure (PAP) are relatively recent to the literature. Driven in part by prior large epidemiological or observational studies of obstructive sleep apnea (OSA) and associated comorbidities,[6-10] these large-scale trials[1-3,11-13] examined the effects of PAP on comorbid outcomes, OSA outcomes and/or preventative effects for associated comorbidities such as cardiovascular, metabolic and neurological outcomes. Whereas such trials would expectedly provide the field with confirmatory evidence and advance the cycle of research for translation to practice, there have instead been questions raised about the validity of the results due to design and methodological concerns. PAP adherence has consistently been an area of concern for many of these trials, expressed clearly in noteworthy editorials that have accompanied, or followed, the publication of the large-scale trials of PAP.[14-19] This review will use the recent large-scale trial experience to (1) identify opportunities for increasing rigor,

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reproducibility and transparency of forthcoming and future large-scale, prospective trials of PAP effects and (2) set forth "best trial practices" that directly address PAP adherence while also considering key methodologies and opportunities relative to implementing health behavior strategies embedded within a larger trial design.

Large-scale Clinical Trials of PAP

In a systematic database search of PubMed Plus, Scopus and ClinicalTrials.gov that employed a keyword search strategy (OSA, continuous positive airway pressure [CPAP], randomized controlled trial [RCT] or trial) with delimiters for adult and publication date from 2000 to current [February 1, 2020], six trials were identified that additionally met criteria for: (1) the large-scale definition employed herein, (2) an objective measurement of PAP use/adherence, and (3) reported PAP use in the primary results publication (Table 1). The majority of excluded trials did not meet the review-specific large-scale definition for sample size or outcome interval duration or failed to fully report PAP use with the primary results. Across the included trials, PAP use ranged from 2.3 – 5.0 hours/night (mean or median). In trials reporting a PAP adherence criterion, approximately half of the samples met the commonly reported PAP adherence criterion of ≥ 4 hours/night. The trial samples were characteristically similar with the exception of two trials that had target populations without excessive daytime sleepiness[12] (i.e., by Epworth Sleepiness Score criterion) and/or minimally-symptomatic individuals with OSA[2] (i.e., absence of other patient-reported OSA symptoms). Studied samples were predominantly male, middle-aged, obese adults with moderate to severe OSA. All trials set forth a primary objective to evaluate PAP effects, absent explicit use of the term, "efficacy." PAP was compared to at least one other exposure condition, to evaluate the primary outcome assessed at or after

three months of exposure. Primary outcome results were largely negative, or supportive of the null hypothesis, across the trials.

Evaluation of efficacy, or the true biological effect of a treatment,[5] necessitates exposure to the test and comparator condition(s) to permit the exploration of patient-reported outcomes and/or clinical endpoints that are the efficacy outcome(s). Efficacy is evaluated in the trial setting wherein internal validity is prioritized, notably to the detriment of external validity, or the generalizability to practice.[20] Evaluation of effectiveness, or outcomes of the test and comparator relative to usual, real-world conditions, may similarly examine biomedical end-points but, by design, prioritize external validity for addressing practice and policy priorities.[20] Effectiveness is the "effect of a treatment when widely used in practice."[5]

The identified large-scale trials of PAP all report a primary objective to evaluate the effect of PAP on a primary endpoint and report designs and analytical methods (e.g., intention-to-treat) consistent with efficacy evaluation. Yet, when the published protocols and primary results with supporting documents (i.e., supplement, appendix) are carefully scrutinized, the methodologies and procedures specific to the PAP exposure condition are likened to protocol methods consistent with effectiveness evaluation. Such methods are reflective of standard practice, or usual care. For example, a trial that reports providing participants with contact information for device troubleshooting after providing standard OSA and PAP patient education, including device set-up and mask fitting for longer large-scale trials, subsumes participants will acknowledge and recognize specific barriers to PAP use and then initiate contact. This example is more consistent with standard practice and is thereby better aligned with effectiveness evaluation wherein the "effect of treatment in practice" is the trial objective. While effectiveness trials are imperative to the field, efficacy evaluations cannot, and should not be

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forgone, as knowledge of PAP efficacy is central to defining treatment standards of OSA by varied outcomes, including comorbid outcomes of physiological and clinical importance. Furthermore, efficacy evaluations from randomized trials are viewed as among the strongest evidence towards answering questions of causality (i.e., does OSA cause comorbid outcomes of clinical importance).

Rigor and Reproducibility of PAP Adherence Protocols in Large-scale Trials of PAP

Critical insights from the large-scale PAP trials published to date provide the field with an opportunity to consider how efficacy trials will need to explicitly address PAP adherence within the larger trial protocol to better meet the requirements for rigor and reproducibility as defined by National Institutes of Health (NIH)[21] and similarly emphasized by other federal agencies.[22,23] Trials included herein were designed by teams of interdisciplinary scientific investigators with relevant expertise (Table 2) and supported by at least one federal or regional agency. Resources for trial conduct and oversight (internal and external) were clearly explicated in half of the trial reports,[1,3,13] suggesting careful attention to trial operations that is consistent with the safe, ethical and rigorous conduct of efficacy trials.

There are noteworthy gaps, specific to PAP exposure and PAP adherence protocols, across the included trials that can be leveraged for optimizing PAP adherence in the next generation of large-scale trials of PAP efficacy. For example, an absence of evidence-based behavioral approaches to support PAP use was observed. Some of these gaps are likely attributed to the state of PAP adherence science at the time of planning and conducting the trials. Other gaps may be relative to a myriad of contributors including the absence of clear guidance and/or expectancies for reporting efficacy trial PAP adherence protocols at the time of grant submission and subsequent publication(s) related to the trial.

Methods specific to PAP adherence were abstracted from all available published sources for each trial, including primary results publications, design and methodology publications, publicly-accessible protocols, trial registry data, grant databases (e.g., RePORTER for NIH-funded studies), and secondary results publications if available (Table 3; see online supplement for detailed methods). Corresponding authors identified on the primary results publication were also contacted when published or publicly-available sources lacked information or data specific to PAP adherence methods reported in Table 3. Sorting the reported PAP adherence methods by study period revealed important similarities and differences between these trials for PAP adherence protocols (Box 1; Box 2).

PAP Adherence Criterion

All trials but one[13] identified a PAP adherence criterion, most often defined in the analysis or results section of the respective published papers. This criterion was consistently reported as ≥ 4 hours/night of average PAP use without explicit rationale. There were no methodological details provided for the specified protocol periods during which the criterion was to have been met; and, if the criterion was not met in any specific interval, there were no reports of specific PAP adherence protocols that were employed other than "study contact was initiated." All trials reported designated visits at which time PAP adherence was electronically retrieved or downloaded. Two trials[1,3] reported using a PAP adherence criterion to guide study contact with participants; these interactions were either by phone and/or at an additional research visit to address low PAP adherence. No protocol-based, pre-specified actions were reported for the low PAP adherence interactions.

Trial PAP Exposure ≤ 4 Months & Adherence Protocols

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All trials reported that mask-fitting, equipment review and education were provided by trained or experienced study personnel. Only one trial reported the educational approach employed with participants, using three education modalities to deliver the information.[13] No trials reported specific educational content that was provided to the trial participants. Mask and/or humidification choice was prioritized relative to adherence in one trial[2] while others specified that humidification and "best-fit" mask were provided.[3,13] In some trials,[1-3,11] trouble-shooting, "support for adapting to PAP" and "advice" were reported as protocol activities in the first several weeks to four months.

Trial PAP Exposure > 4 Months & Adherence Protocols

All included trials except one[13] assessed a primary endpoint with PAP exposure greater than four months. The SAVE trial[3] was the only trial that reported using a specific PAP adherence protocol extending beyond four months. This trial, with a large number of sites extending around the globe, was also unique in that a centralized study structure, Sleep Laboratory Core, was charged with monitoring PAP use across sites and provided centralized expert advice to sites when PAP adherence was below the study-defined criterion. The SAVE trial also employed PAP use, leak and residual apnea-hypopnea index (AHI) criteria from PAP initiation to study end with PAP remote monitoring.[3]

When the trials are considered collectively, PAP adherence protocols are generally under-reported, which limits reproducibility and impacts evaluation of the rigor for the reported work. This weakness limits the potential for other investigators to address the challenge of optimizing PAP adherence in subsequent large-scale PAP trials. The included trials report methods that are seemingly consistent with earlier published clinical practice guidelines[24] and with what the field considered "standard practice" at the time of these trials. The PAP

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adherence achieved in the included trials is therefore not unexpected given 1) the modest trial

PAP adherence protocols and 2) the observation that across PAP clinical trials and clinical trial

follow-up observational studies, the weighted average of PAP use was 4.46 hours/night and

average non-adherence rate was 36.3%.[25] These observed metrics of PAP adherence are

consistent with other reviews that have addressed summary PAP adherence across studies.[26,27]

The obvious concern is that this level of PAP adherence is sub-optimal for a rigorous

assessment of efficacy.

The overwhelmingly negative results across the large-scale trials coupled with the

minimalist approaches to PAP adherence within the conduct of the efficacy trials provide the

evidence and the necessary motivation for future large-scale trials to carefully design and report

PAP adherence protocols in great detail. These protocols will need to use the current PAP

adherence evidence to potentiate higher PAP adherence across study participants. Such

adherence protocols should be embedded within the larger trial protocol to ensure

reproducibility and strengthen rigor relative to PAP adherence. This approach will best position

large-scale efficacy trials to test PAP by providing results that are unbiased relative to

adherence.

State of the Science: PAP Adherence

Since the earliest large-scale trial[1] was conducted, PAP adherence intervention studies

have been increasingly represented in the literature. The body of evidence has recently been

systematically examined, resulting in a meta-analysis[4] that supports the current American

Academy of Sleep Medicine's clinical practice guideline for the PAP treatment of adults with

OSA.[28] The meta-analyses addressed PICO (Population, Intervention, Comparison, Outcome)

questions of which eight of the 11 questions included PAP adherence as an outcome (Box 3).

The cumulative set of reviewed evidence (n=1,512) was reduced to a final set of 184 studies that addressed one or more of the PICO questions;[4] for each PICO question, a sub-set of studies were eligible for meta-analysis. With a pre-specified clinical threshold of significance for the PAP adherence outcome set at 0.5 hours/night or 10% patient use > 4 hours/night, the results of the meta-analysis support the accompanying practice guidelines.[28] Explicit PAP adherence interventions addressed by the meta-analyses and subsequent practice guidelines include educational, behavioral and tele-monitoring recommendations; on average, these interventions, individually, result in an estimated PAP use effect of 1.0 hour/night (Figure 1). The available cumulative evidence provides guidance for designing evidence-based PAP adherence protocols for future large-scale efficacy trials.

Advancing PAP Adherence Protocols in Large-scale PAP Trials

Recommendations for using evidence-based PAP adherence protocols in large-scale trials include 1) tele-monitoring, 2) behavioral approaches and 3) education. In addition, other methodologies can be leveraged to improve PAP adherence, including 1) using a PAP run-in period and 2) considering sampling criteria specific to PAP adherence. Due to the well-recognized heterogeneity in PAP adherence behavior and factors that are associated with this behavior,[26,27] a multi-component PAP adherence protocol is best-suited for large-scale trials. Investigative teams will need to carefully balance the complexity and required expertise for these protocols with feasibility and resource considerations. This is particularly poignant as the large-scale PAP trials to date have been summarily under-funded (Box 4).

Tele-monitoring

With the advancement of PAP technology by industry, the field is well-positioned to objectively measure PAP adherence and capitalize on near real-time treatment usage and effectiveness data. Future large-scale trials will leverage this technology in PAP adherence protocols to guide PAP interventions. Study-defined criteria for PAP adherence by study intervals (e.g., first week, first month) and by near real-time intervals (e.g., within consecutive days) can be established. This approach, if adjoined with a response-to-PAP use plan (e.g., tele-coaching), supports early intervention for PAP non-adherence[29] and conservation of resources within the trial. This is important as evidence from observational studies has consistently identified that early PAP use is a predictor of long-term PAP use;[30,31] similarly, analyses of PAP trial data has demonstrated the same.[32,33] The recommendation for employing a tele-monitoring and response-to-PAP use protocol within large-scale trials also potentiates engagement which is a relevant consideration for improving or changing health behavior(s).[34-37] Employing both participant- and trial-facing applications and/or web-based portals that may be industry-supported, or study-specific, are strategies that support PAP use during the active engagement period;[37-42] importantly, PAP use may attenuate after engagement concludes.[38] When using industry-supported applications and tele-monitoring platforms, industry partners bring knowledge on how these digital solutions work and experience from other trials to support streamlined data acquisition and integration.

When designing the PAP adherence tele-monitoring protocol, the following factors should be carefully considered: 1) pre-defined usage thresholds in industry-supported tele-monitoring solutions and the alignment of these thresholds with trial-defined usage criterion; 2) centralized and/or site level tele-monitoring and response-to-PAP use responsibilities and protocols; 3) resources necessary to maintain tele-monitoring protocols; 4) participant burden,

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including ethical considerations for informed consent language addressing the schedule of interactions (i.e., intensity); and 5) innovative approaches that can be employed to automate tele-monitoring response actions by the trial team, whether at a centralized or site-level, with specific intention to deliver response actions by communication methods that are defined by participant preference (e.g., video visits, text messaging, online chat access as opposed to telephone calls and face-to-face visits).

Behavioral Approaches

Several behavioral approaches for PAP adherence can be considered for large-scale trials. The field of behavioral sleep medicine has significantly grown over the past 10 years as has the inter-disciplinary field of experts in behavioral sciences who can provide required expertise for planning and delivering behavioral approaches for PAP adherence in large-scale trials. Determining which behavioral approach(es) to embed in a large-scale PAP trial will be guided by the evidence at the time of planning the trial, expertise of the trial team, schedule of research visits and/or interactions, and the target population/sample of the trial.

Behavioral interventions tested with positive effects for PAP adherence to date have been delivered at the outset of PAP treatment (e.g., at PAP initiation) to PAP-naïve adults with OSA.[43-47] Included in this review, one large-scale trial indicated by corresponding author communication that motivational or cognitive strategies were employed to encourage PAP adherence without further details; this protocol activity was not reported in the study publications.[11,48] Based on the publications and corresponding author communications, it is unknown if other trials included in this review also used behavioral approaches for PAP adherence. It is recommended that these behavioral protocol activities be fully-reported by future large-scale trials. Reporting guidance that can be used include the SPIRIT guidelines[49]

(Standard Protocol Items: Recommendations for Interventional Trials) and TIDier guidelines[50]

(Template Intervention Description and Replication checklist and guide; both available at

https://www.equator-network.org/. Other important considerations for embedding behavioral

approaches include: 1) timing and format of delivery; 2) centralized and/or site-level oversight,

training and management of behavioral approaches; 3) resources required to maintain delivery

of behavioral approaches during trial execution, including fidelity assessments; 4) participant

burden, including informed consent language addressing the schedule of interactions (i.e.,

intensity); and 5) including a behavioral scientist as a team member with expertise specific to

the phenomenon of PAP adherence, or health behavior.

Education

Disease and treatment education is a practice norm at diagnosis and treatment initiation

in OSA, consistently set forth by consensus[24] or strong recommendation.[28] Though the effect of

education on PAP adherence is notably modest,[4] it is an essential component of behavior

change.[51] Education about OSA and PAP was a consistent protocol activity in the trial setting

based on our review of large-scale PAP trials. Considering the diverse (e.g., geographic,

literacy, culture) nature of participants in PAP randomized trials, and to minimize the risk of

excluding sub-groups with different or special needs (e.g., language, visual impairment, low

health and general literacy), the content and delivery mode(s) of education materials should be

designed with attention to these needs. Recent evidence suggests commonly used sleep

education materials that are widely available from American Thoracic Society and American

Academy of Sleep Medicine have high health literacy demands, requiring high school level or

higher education.[52] Understandability and clear communication indices of the materials were

also scored low.[52] The Centers for Disease Control and Prevention and Agency for Healthcare

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Research and Quality provide explicit guides and information for designing and delivering health information to varied audiences;[53,54] trial teams are urged to use such resources when designing educational materials (see also: http://centerforhealthguidance.org/health-literacy-principles-checklist.pdf). If selecting publicly- or commercially-available materials for trial use, evaluation of the materials with more than readability procedures is important (e.g., Flesch-Kincaid tests). Other recommendations include 1) consulting with or having a team member with education expertise specific to the delivery of health information; 2) pilot testing trial education materials with a representative group of patients and revising materials as indicated; and 3) exploring multi-modal delivery of educational materials to trial participants at varied study intervals so as to "off-load" demands at the outset of PAP initiation.

Incentives

The behavioral economics framework assumes that people make decisions with error and "nudges" are needed to increase the likelihood of good decisions, or decisions that are in a person's best self-interest.[55,56] Nudges can take many forms including, but not limited to, incentives and rewards which may be financial in structure. Using incentives and rewards as an intervention approach for health behavior is an emerging area of study across the literature; yet, a relatively small body of evidence exists for PAP adherence in patients and no studies, to our knowledge, report on incentives directed to research sites/teams for PAP behavioral intervention delivery. Use of incentives in large-scale PAP trials for participants and/or sites and staff must be considered with caution as the effects, ethics and methodologies are not well-understood. As has been recently acknowledged,[57] financial incentives do not always work. There are a myriad of details that must be understood before embedding such incentives in a study; "the devil is in the detail, because the magnitude of effects differs substantially based on

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the nature of the behavior, the size of the incentive, the population involved, the social context and the design [of the incentive]."[58]

If, however, incentives and rewards are conceptualized as non-financial, the ethical concern for coercive effects and distributive inequity are lessened.[58] Such incentives and rewards, for example, might include de-identified "performance" metrics with comparative ratings and messages (e.g., "Kudos Reports"), goal tracking worksheets/visualizations to explicate incremental progress with digital badges and personal rewards-to-self that are based on self-appraisal metrics. These are but a few examples derived from both behavioral economics theory and the existing PAP adherence evidence that address goal-directed behavior change, engagement and motivation. Though the state-of-the-science for financial incentives for PAP adherence is yet under-developed, incentives are likely to be a consideration for future large-scale trials with scientific advancement in behavioral economics for sleep and PAP adherence.[59]

Run-In Methods

Randomized trials may employ a run-in, or a pre-randomization exposure period to the active or placebo condition(s), in order to exclude non-adherers, placebo responders, active condition non-responders or active condition intolerance.[60] Run-in methods are not uncommon in industry and/or pharmacologic trials, but are less common in PAP trials,[46] including large-scale trials.[3] Employing run-in periods is not without controversy however, as external validity is compromised when a run-in period is used.[61] This is because the representativeness of the trial sample will necessarily differ from the clinical target population. Yet, when efficacy is the primary aim of the trial, internal validity is prioritized unlike in effectiveness trials. Another concern to be carefully considered in implementing a run-in period is the impact that a positive

PAP experience, and positive treatment effects, may have on cross-over rates, wherein subjects having done well with PAP and then randomized to the comparator condition may decide to obtain PAP therapy outside the trial. Similarly, in trials where active PAP is compared to placebo, or sham PAP, and sham PAP or a modified PAP profile (e.g., mask/headgear only) is used during the run-in, subsequent use of PAP, or adherence, may be affected by the run-in experience. For example, cognitive perceptions of PAP are different (e.g., lower outcome expectancies) with sham versus active PAP.[62] In addition, when a placebo is the trial comparator such as with sham PAP, the risk of un-blinding must be carefully navigated when using run-in methods.

There are important considerations when planning a run-in period for a large scale PAP trial which include: 1) monitoring run-in data to support fully reporting the number of run-in exposures conducted, failed run-in rate, and run-in participants' (failed and completed) characteristics compared to the trial sample; 2) determining and reporting run-in PAP adherence criteria which should be consistent with the post-randomization PAP adherence criteria if the run-in is designed to reduce the overall risk of bias introduced by non-adherence; and 3) determining if failed run-in will be repeated based on pre-specified criteria. Most trials that have reported run-in periods have not adequately described the run-in protocol nor run-in results to address concerns about sample representativeness.[63] As of the writing of this review, there are no published guidelines for run-in period reporting; until such are available, large-scale trials that employ a run-in period will need to carefully consider the implications of the run-in methods on the overall trial results. Statistical expertise and trial methodologists are recommended to best guide these considerations.

Sampling Criteria Methods

A robust evidence set exists that addresses influential factors on PAP adherence.[26,27,64] The evidence suggests that these factors may be measurable at baseline in the efficacy trial setting and employed as sampling criteria to potentiate PAP adherence. When considering this approach it is important to reflect on how the selected factors may impact on enrollment rates and trial sample characteristics. The measurement, or screening, for such factors must also be feasible using validated instruments. Consideration must be given to the burden of measurement, ethical decision-making for sampling criteria and timing of measuring such factors. If predictive factors of PAP adherence are employed as sampling criteria to potentiate PAP use in the efficacy trial setting, this will necessarily have implications on generalizability. For this reason, investigators might examine site-level target population characteristics and determine the effect of imposing the sampling criteria specific to PAP adherence on sample accrual and characteristics at the trial design phase. This approach may best reduce sampling feasibility concerns while also providing data-based insights for statements of generalizability.

Future large-scale trial teams will need to remain abreast of emerging evidence for PAP adherence interventions and employ innovative **and tested** approaches to best optimize PAP adherence in the setting of an efficacy trial. No single approach to PAP adherence interventions within any trial is recommended but rather, embedding evidence-based interventions that are aligned with:

- trial team expertise (see next section, Trial Team Composition),
- the *a priori* threshold for PAP adherence for the end-point,
- the estimated PAP use in the target population based on prior published observational studies or pilot trials, and
- trial resources.

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Both investigators and funding agencies will necessarily embrace increasingly complex trial designs that necessitate thoughtful trial planning periods and nuanced trial management plans/processes and structures for successfully conducting these trials.

What Does the Future of Large-scale Trials of PAP Look Like?

Designing and conducting the next generation of large-scale PAP trials is a critical consideration for the field based on recent trial experiences. Explicit opportunities that are germane to addressing the rigor and reproducibility aspects of large-scale prospective PAP trials and thereby reducing concerns for internal validity specific to PAP adherence include (1) trial team composition, (2) operational structure, (3) protocol-within-protocol design, (4) protocol execution, and (5) trial reporting. By setting forth these recommendations for large-scale PAP trials, the stage is set for substantive dialogue among investigators, funding agencies and trial partners (e.g., industry, technology/innovation) in order that "best trial practices" for large-scale PAP adherence efficacy trials are commonplace.

<u>Trial Team Composition</u>

Adherence to a new health behavior, such as in the trial setting with assignment to PAP among treatment-naïve adults with OSA, is challenging for both participants and the trial team. Trial investigators and site staff may have substantial clinical and/or practical experience with introducing PAP and managing PAP adherence but this is not necessarily transferrable to a trial setting. For example, unlike research participants who should have equipoise about receiving PAP therapy, patients presenting for clinical care, by virtue of seeking care, are motivated to initiate treatment. Also unlike the clinical setting, time-to-adherence is of high importance in large-scale PAP trials due to pre-defined outcome assessments and study resource-constraints.

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Active adherence interventions that consist of more than device/equipment trouble-shooting and advice may not be well-developed skills among staff and investigators with primarily practice-based experience who manage a wide range of sleep disorders and treatments.

Behavioral science is a distinct field. While investigators of these large-scale trials may have practical health behavior experience, this does not necessarily equate to depth and breadth of knowledge and application of behavioral health interventions that are scientifically-derived; nor does such practical experience equate to measurable performance outcomes as is necessary in these trials. Trial team composition must therefore be carefully considered at the earliest planning stages of the trial. At the investigator level, a behavioral scientist with expertise in PAP adherence will ideally be included and lead the protocol for PAP adherence. This approach will potentiate a scientifically-sound protocol specific to PAP adherence and an investigator with committed time and focus for this methodological and implementation work.

Another key consideration for team composition is successfully recruiting and retaining site-level staff members that may, or may not, have relevant experience but who are amenable to learning and consistently applying behavioral protocol activities as prescribed. Retention of staff ensures consistency of contact between the trial site and participants. This is similarly applicable if a centralized structure, or core, is designated for PAP adherence in the trial. Staff with strong communication skills, including skills for developing rapport and active listening, are imperative to the success of delivering health behavior interventions such as those with positive effects for PAP adherence (see Figure 1). These team composition recommendations are directly supportive of behavioral and implementation science approaches that address partnership, engagement and collaboration as the cornerstone of health behavior change,[34,65,66] including recent work in the PAP adherence field addressing technology-driven patient

engagement,[37] a vision for patient-centered approaches to OSA and PAP management[67] and emphasis on team approaches for PAP adherence.[68]

The introduction of stakeholder advisory boards that may include patients, community leaders and/or clinical providers has emerged as a research priority in many countries, including the U.S., U.K., Canada and Europe.[69] Designing PAP adherence protocols for employ within an efficacy trial with patient stakeholders has yet to be reported to our knowledge; in fact, patient engagement across published randomized controlled trials has been limited to date.[69] However this approach may be an innovative opportunity for large-scale PAP trials. Patient preferences for protocol activities, for example communication frequency and mechanism, can be accounted for from the outset of the trial with input from patient stakeholders, or advisors. This may potentiate participant acceptability of the PAP adherence methods and protocols[70] and thereby, trial enrollment and retention. Resources for researchers considering engagement approaches at any study phase, but as suggested here at the trial design level, can be found at Patient Centered Outcomes Research Institute website

(https://www.pcori.org/engagement/engagement-resources/Engagement-Tool-Resource-Repository).

Operational Structure

From the outset of trial planning, the investigative team should consider the development of a PAP Adherence Core, a centralized operating structure specific to PAP adherence. Consistent with the more commonly reported trial structure of a Sleep Reading Core or Sleep Laboratory Core, the PAP Adherence Core investigators who have scientific and implementation expertise in health behavior change and PAP adherence will design protocols specific to PAP adherence that are embedded within the larger trial protocol. Oversight for

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adherence protocols is a central responsibility of the Core, including training, protocol fidelity and quality of protocol implementation. By centralizing these functions among a dedicated Core, the necessary knowledge and skill to support site-based staff and investigators for PAP adherence can be efficiently managed. Increasingly focused intervention approaches to PAP adherence that are evidence-based can be designed with an expert core; these approaches can be carefully aligned with the larger trial protocol (i.e., protocol-within-protocol, or a nested protocol). In order for this approach to be successful, the PAP Adherence Core investigators must be engaged with the trial investigators/team from the earliest point possible in the design of the trial and function as active trial team members. This approach will ensure that all trial activities that bear influence on participants' use of the test condition will be addressed from a behavioral perspective from design through results reporting.

Trial Execution

A dedicated PAP Adherence Core will necessarily design and deliver training specific to PAP adherence protocols. As most large-scale trials include a Training or Education Committee, the Core will work collaboratively with the larger Committee to ensure all trial-specific standards and expectations are met with delivery of PAP adherence training. In the setting of large-scale trials that have numerous geographically disperse sites, training approaches will need to be increasingly innovative yet effective in the delivery to conserve trial resources (Box 5). Areas of training consideration by the Core will include: training content, delivery modes and styles of training content, performance standards relative to training sessions and ongoing monitoring performance standards, certification and re-certification of staff for all procedures. Contingency training plans for newly hired staff and for those previously

certified staff who demonstrate a need for booster training identified during the protocol fidelity monitoring procedure is also recommended.

Fidelity monitoring procedures should be designed by the PAP Adherence Core and monitoring intervals and procedures established in collaboration with relevant trial entities, most likely to include the Data Coordinating Center (DCC). By establishing partnerships between the Core and the DCC which is a cornerstone of efficient data monitoring in large-scale trials, fidelity monitoring of PAP adherence intervention protocols and performance metrics for quality protocol delivery will be meticulously tracked and communicated to the Core and study investigators. Thresholds for fidelity and protocol delivery, established by the Core and trial investigators, will subsequently guide remediation, or booster, training decisions, adjustment of monitoring intervals, and trial site evaluation and feedback. Though these thresholds are directly aligned with sub-optimal performance, the Core will also ideally recognize and reward consistent performance above the threshold and exceptional performance.

<u>Trial Reporting</u>

Reporting of PAP adherence protocols in large-scale trials should be included with the methodology publication and/or with the primary results publication. Though page limitations may be prohibitive of a complete reporting of PAP adherence protocols, supplemental or appendix materials can be used to fully report the protocol. To support both rigor and reproducibility guidelines, a minimum description of PAP adherence protocols should include:

- All intervention approaches employed by protocol period/interval

- Complete description of all intervention methods

- PAP adherence criterion and rationale

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- Measurement methods of PAP adherence employed and measurement intervals

- Description of training for delivery of intervention(s)

- Fidelity monitoring plan including performance thresholds at study- and site-level

When reporting trial results, PAP adherence should be reported as a summary continuous research variable (mean hours/night) at trial end-point and by study interval for trial-relevant periods (e.g., scheduled recurrent research visits). Because PAP adherence is usually not normally distributed, reporting PAP use by only mean and standard deviation can be misleading. Therefore, PAP adherence criterion for the trial should also be reported as a frequency at trial end-point and by study interval at trial-relevant periods. Any pre-specified per-protocol analyses based on PAP adherence should also be reported with trial results. Protocol-based results that are of importance to report include summary fidelity results at the study-level and training completion rates, including booster/remediation training conducted throughout the trial period.

Conclusion

Prospective efficacy trials are requisite to setting forth treatment standards and guidelines and generate causal effects knowledge. Though innovative comparative methodologies that employ big data and precision health scientific methods are likely to also contribute treatment standards and guidelines, prospective efficacy trials of a large-scale nature will continue to be necessary. Recent efficacy trials of PAP therapy have been challenged by concerns for validity relative to low PAP use, or non-adherence. Careful scrutiny of these precedents shed light on opportunities to address PAP adherence in forth-coming and subsequent trials. In order that PAP adherence is optimized, evidence-based protocols focused

on PAP use should be embedded within the larger trial protocol. In doing so, investigators will

need to carefully balance numerous factors relative to feasibility, ethical trial conduct and overall

study rigor. Important considerations are highlighted in this review to facilitate dialogue in the

field for "best trial practices" that are specific to PAP adherence, including reporting guidance at

the time of funding application, methodology and results/protocol publications. It is with

attention to these opportunities that there will be reduced concern for the validity of large-scale

PAP trial results and these trials will meet expectancies for rigor and reproducibility.

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Figure 1. Evidence-based PAP Adherence Interventions and their Estimated Improvement for PAP Adherence.

Caption. Adapted with permission from Patil, et al., 2019. Estimated effects for PAP adherence (i.e., use) are meta-analyses results reported in Patil, et al., 2019.[4]
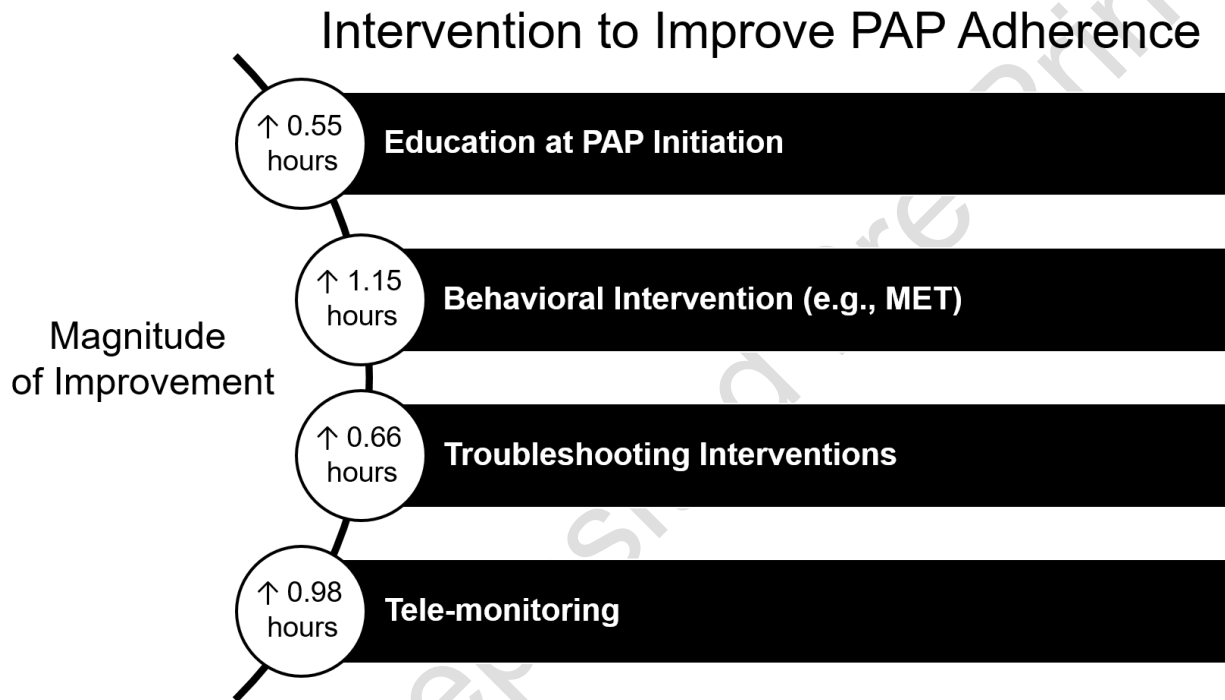
Intervention to Improve PAP Adherence

↑ 0.55 hours — **Education at PAP Initiation**

↑ 1.15 hours — **Behavioral Intervention (e.g., MET)**

Magnitude of Improvement

↑ 0.66 hours — **Troubleshooting Interventions**

↑ 0.98 hours — **Tele-monitoring**

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Table 1. Description of Published Large-scale Trials (n=6)

Trial (Project Years)	Location (Sites)	Primary Endpoint	Follow-up	Study Sample	Intervention (N)	Comparator (N)	PAP Use Criterion	Adherence h/night	Adherence % ≥4 h	Primary Outcome (+ or -)
APPLES[1] 2003 - 2008	US (5)	Neurocognitive function	6-mo	OSA patients	CPAP (n=556)	Sham-PAP (n=542)	≥4	4.2	56.2%	–
Spanish Cohort[2] 2004 - 2009	Spain (14)	Incident HTN & CV events	3-yr	OSA patients (Non-sleepy)	CPAP (n=358)	No treatment (n=367)	≥4	5.0	64.4%	–
MOSAIC[3] 2006 - 2010	UK/Canada (10)	CV risk score	6-mo	OSA patients (Non-sleepy)	CPAP (n=195)	Usual care (n=196)	≥4	2.4	NR	–
HeartBEAT[4] 2010 – 2012	US (4)	24-hr BP	3-mo	Cardiology patients with OSA	CPAP (n=106) Oxygen (n=106)	Lifestyle education (n=106)	NR	3.5	NR	+
SAVE[5] 2008 - 2015	Australia, China, New Zealand, India, Spain, US, Brazil (89)	MACE	4-yr	CVD patients with OSA	CPAP (n=1359)	Usual care (n=1358)	≥4	3.3	42%	–
ISAACC[6] 2011-2018	Spain (15)	MACE	≥1-yr	ACS patients with OSA	CPAP (n=633)	Usual care (n=631)	≥4	2.8	37.5%	–

Notes. APPLES, Apnea Positive Pressure Long-term Efficacy Study; Spanish Cohort Trial; MOSAIC, Multicenter Obstructive Sleep Apnea Interventional Cardiovascular trial; HeartBEAT, Heart Biomarker Evaluation in Apnea Treatment; SAVE, Sleep Apnea Cardiovascular Endpoints study; ISAACC, Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome.

Abbreviations- Yr, years; mo, months; h, hours; CPAP, Continuous Positive Airway Pressure; OSA, Obstructive Sleep Apnea; NR, Not Reported; HTN, Hypertension; CV, cardiovascular; MACE, Major Adverse Cardiovascular Event; CVD, Cardiovascular Disease; ACS, Acute Coronary Syndrome.

Table 2. Scientific Trial Team Members by Discipline or Specialty[†]

Discipline Involved	APPLES	Spanish Cohort	MOSAIC	HeartBEAT	SAVE	ISAACC
Sleep Medicine	+	+	+	+	+	+
Respiratory Medicine	+	+	+	+	+	+
Clinical Trialist and/or Statistics	+	-	+	+	+	+
Study-Specific Discipline Relative to Biomedical Focus	+	-	-	+	+	+
Behavioral Science	-	-	+	-	-	-

Notes. APPLES, Apnea Positive Pressure Long-term Efficacy Study; Spanish Cohort Trial; MOSAIC, Multicenter Obstructive Sleep Apnea Interventional Cardiovascular trial; HeartBEAT, Heart Biomarker Evaluation in Apnea Treatment; SAVE, Sleep Apnea Cardiovascular Endpoints study; ISAACC, Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome.

[†]*Identified by author affiliation(s) in methodology and/or result publication.*

Table 3. Concentration of Methods Specific to Positive Airway Pressure Adherence by Large-scale Trial Study Period (n=6)

Trial Name	Screening Criteria[†] Or Other Pre-Randomize Methods	Random Assignment[‡]	PAP Initiation	Wk 1	Mo 1	> Mo 1
					PAP Exposure →	
APPLES	+	+	+	++	+	++
Spanish Cohort Trial	−	−	++	−	−	−
MOSAIC	+	−	++	−	+	+
HeartBEAT	+	−	+++	−	−	−
SAVE	+++	+	+++	++	+++	++
ISAACC	+	−	+++	++	++	+

Notes. APPLES, Apnea Positive Pressure Long-term Efficacy Study; Spanish Cohort Trial; MOSAIC, Multicenter Obstructive Sleep Apnea Interventional Cardiovascular trial; HeartBEAT, Heart Biomarker Evaluation in Apnea Treatment; SAVE, Sleep Apnea Cardiovascular Endpoints study; ISAACC, Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome.
[†]Inclusion and Exclusion Criteria that are specified for PAP adherence in methodology and/or result publication and/or supplemental/appendix materials and/or publicly-availably protocol materials.
 [‡]Reported protocol activities specific to PAP use/initiation/adherence conducted concurrently with randomization.
(−), zero reported method; (+), 1 reported method; (++), 2 reported methods; (+++), 3+ reported methods. See Online Supplement for detailed reported methods.

Abbreviations – PAP, Positive Airway Pressure; Wk, Week(s); Mo, Month(s).

Box 1: Consistent PAP Adherence Methods in Large-scale PAP Efficacy Trials (n=6)

- **Exclusion Criteria**
    - ✓ Prior PAP use
- **PAP Initiation**
    - ✓ By trained (or experienced) study personnel
- **PAP Use Measurement**
    - ✓ Objective at varied study intervals

Box 2: Exceptional[†] PAP Adherence Methods in Large-scale PAP Efficacy Trials

- **Exclusion Criteria**
  - ✓ Other household member w/PAP use[1-3]
- **Other Criteria at Screening or Enrollment**
  - ✓ 1-wk Run-in with ≥ 3 hours/night average use[3]
- **Random Assignment**
  - ✓ 20-minute Acclimatize-to-PAP session[1]
- **PAP Initiation**
  - ✓ Education about OSA and PAP provided by verbal, audio-visual and written methods[13]
  - ✓ Behavioral sleep medicine specialist provided pre-treatment information about PAP[11*]
  - ✓ Mask and humidification choice[2]
- **Exposure Intervals**
  - ✓ PAP use criterion during auto-PAP titration period[3]
  - ✓ PAP FAQs for study staff to reduce risk of un-blinding participants (sham vs CPAP)[1]
  - ✓ Core Sleep Lab remote review of PAP use, leak data at regular defined intervals[3]
  - ✓ Core Sleep Lab provide corrective advice to sites, study team as needed[3]
  - ✓ Sleep hygiene advice specified by investigators as relevant to PAP adherence (alcohol and tobacco use, short sleep duration)[11]
  - ✓ Week 1 phone f/u[1,3]
  - ✓ Week 2 phone f/u[11]
  - ✓ Phone f/u based on PAP usage criterion[1,3]
  - ✓ Motivational and cognitive strategies used to increase PAP use[11*]

*Notes. [†]Exceptional defined as reported in ≤50% of included trials. *Not reported in published methodology or results; provided by corresponding author in response to electronic mail query requesting any additional protocol activities specific to PAP adherence.*

Box 3. Summary of PICO Questions and Evidence Density and Quality for Meta-analyses of PAP Adherence Outcome in Patil, et al. 2019[4]

Q4: In-lab vs. Ambulatory PAP titration based on 10 RCTs of high quality

Q5: Auto-titrating vs. continuous PAP based on 23 RCTs of moderate to high quality

Q6: Bi-level PAP or auto-Bi-level PAP vs. CPAP based on 4 RCTs of low quality

Q7: Modified pressure profile vs. no modified pressure profile based on 6 RCTs of low quality

Q8: Oral vs. nasal PAP mask based on 2 Cross-over RCTs and 1 RCT of low quality

Q9: PAP with humidity vs. no humidity based on 9 RCTs of low to moderate quality

Q10: Educational intervention based on 7 RCTs of moderate quality **or**
Behavioral intervention based on 6 RCTs of moderate-high quality
vs. No intervention (interventions delivered prior to or during PAP)

- **Troubleshooting + education** intervention based on 9 RCTs of moderate quality was separately meta-analyzed

Q11: Tele-monitor guided intervention vs. no tele-monitoring based on 5 RCTs of high quality

Notes. Abbreviations: PAP, Positive Airway Pressure; vs., versus; RCTs, Randomized Controlled Trials; CPAP, Continuous Positive Airway Pressure.

Box 4: Publicly-reported Funding of Large-scale PAP Efficacy Trials (n=6)

Trial Name	Funding Sources†	Publicly Available Total Costs‡
APPLES	NIH/NHLBI	$14,094,332
Spanish Cohort Trial	Sociedad Española de Neumología y Cirugía Torácica	Not Available
MOSAIC	British Heart Foundation Oxford Radcliffe Hospitals NHS Trust (UK)	Not Available
HeartBEAT	NIH/NHLBI	$3,679,973
SAVE	National Health and Medical Research Council (NHMRC) Philips Respironics (Industry) Respironics Foundation	$8,904,248
ISAACC	ResMed (Industry) Fondo de Investigacion Sanitaria (Fondo Europeo de Desarrollo Regional)	Not available

†Funding source identified in methodology and/or result publication and/or in trial registry; ‡Data retrieved from funding agency database, when publicly-available.

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Box 5. Training Approaches for Site Staff in Large-scale PAP Trials: Leveraging Innovation in Delivery, Format and Style

- **Baseline Protocol Training**
  - ✓ Face-to-Face Delivery
    - ▪ Didactic for general protocol information
    - ▪ Written materials to reinforce didactically delivered content
    - ▪ Diagrammatic materials for protocol scheme, decision-making
    - ▪ Teach-teach back for protocol delivery to participants
    - ▪ Role-play for protocol delivery to participants with peer-to-peer evaluation
    - ▪ Case-based learning with participant scenarios
  - ✓ Review of Manual of Operations (MOP) for PAP adherence protocol
- **Protocol Training Refreshers**
  - ✓ Pocket Card Deck for PAP adherence protocols and procedures
  - ✓ Web-based portal with baseline training materials and access to refresher training materials
  - ✓ PAP adherence protocol and procedure checklists
- **Periodic Booster Training (PBT) and New Staff Training After Baseline Training (NST)**
  - ✓ Web-based synchronous videoconferences: Challenging Scenarios, Case-based Learning approach (PBT)
  - ✓ Web-based asynchronous Case-based learning (PBT)
  - ✓ Web-based or Nudge-based Push Notifications to web-based link: Brief training modules (≤ 5 minutes) (PBT)
  - ✓ Web-based synchronous and asynchronous training sessions (NST)
  - ✓ Peer-to-Peer training within sites with expert staff (NST)
  - ✓ Simulation training by remote access portal/tele-education (NST)

Supplemental Materials

Where to Next for Optimizing Adherence in Large-scale Trials of PAP?

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Supplement Table 1. Large-scale Trials Description of Methods Specific to Positive Airway Pressure Adherence by Study Period						
Trial Name *(chronologic order by publication date)*	**Screening Criteria[†] Or Other Pre-Randomize Methods**	**Random Assignment[‡]**	**PAP* Initiation**	**Wk 1**	**Mo 1**	**> Mo 1**
				Exposure		
APPLES[1]	**Exclusion**: Prior PAP use; Other house member w/PAP use (current or past)	20-min PAP habituation exercise before titration PSG	CPAP dispense by study personnel after titration PSG	**1-Wk:** phone by RS X2 • Ensure use • Manage problems • Protocol guide for PAP FAQs (reduce risk of un-blinding)** Contact w/<4hr/nt use	Regular contact w/<4hr/nt use	Regular contact w/<4hr/nt use **4-Mo**: FTFV w/study physician • PAP use discuss
Spanish Cohort Trial[71]	NR	NR	CPAP dispense at home after PSG or unattend HST at sleep center • 5hr sleep • Leak criteria	NR	NR	NR
MOSAIC[2]	**Exclusion**: Prior PAP use	NR	PAP dispense by study staff after randomize • AutoPAP • Trained staff	NR	**3-Wk** FTFV • PAP f/u	**2-Mo** Phone • Advice • Supplies **4-Mo** Phone • Advice

			• Humidity optional • Mask choice			• Supplies PAP use data download minimum 1X b/w initiation-END • Residual AHI • Air Leaks
HeartBEAT[1][3]	**Exclusion**: Prior PAP use	NR	APAP dispense by site coordinator w/random assign • Auto-titrate X7days • Then set pressure Instruction by coordinator for use of assigned treatment • Humidity • Mask-fit by expert tech Healthy lifestyle & sleep education to both grps by slide presentation, hard-copy of slides, publicly available	NR	NR	NR

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			education materials (AHA): • Regular sleep schedule • Avoid ETOH @bed • Sleep duration 7-8hr/nt			
SAVE[3]	**Exclusion**: Neuro deficit prevent PAP mask apply; Prior PAP use; Other house member on PAP **Other**: 1-wk Sham Run-In to exclude unlikely/ unwilling to adhere to PAP; patients informed of run-in purpose; sham device used; phone call Run-In Day 2-3; run-in criterion	Written information about PAP View DVD: Trial importance & adherence to PAP	APAP dispense by study staff @FTFV • Best mask fit • Humidity • Auto-titrate X7 days • Set pressure • Auto-titrate criteria: ≥3hr/nt average use, average leak <60L/min • If auto-titration criterion not met: • Address issues & repeat titration X7 days	**1-Wk**: Phone RS contact • Manage problems Additional phone contact if problems	**1-Mo**: Remote review of PAP data by Core Sleep Lab • PAP use <3hr/nt • Air leak >60 L/min • AHI>15/hr **1-Mo**: FTFV as needed for PAP problems Core Sleep Lab monitors PAP use, provide corrective advice to sites, study team	**3-Mo & 6-Mo**: Remote review of PAP data by Core Sleep Lab • PAP use <3hr/nt • Air leak >60 L/min • AHI>15/hr **Q6-Mo**: Phone

	≥3hr/nt average					
ISAACC[11]	**Exclusion**: Prior PAP use	NR	In-hospital (enrolled inpatients) APAP by trained nurse followed by fixed pressure PAP Behavioral sleep medicine specialist provided pre-treatment information; motivational and cognitive strategies to increase PAP use employed**	**15-Day**: Phone • Resolve problems • Phone # provided to access study staff any time for PAP problems • FTFV schedule prn	**1-Mo**: FTFV • Adapt to PAP support • Support PAP adhere using cognitive and motivational strategies** • Sleep hygiene advice by sleep unit staff at all scheduled visits; Health behavior advice include avoid evening ETOH, reduce tobacco, avoid short sleep	**3-Mo**: FTFV • Adapt to PAP support • Support PAP adhere

Notes. APPLES, Apnea Positive Pressure Long-term Efficacy Study; Spanish Cohort Trial; MOSAIC, Multicenter Obstructive Sleep Apnea Interventional Cardiovascular trial; HeartBEAT, Heart Biomarker Evaluation in Apnea Treatment; SAVE, Sleep Apnea Cardiovascular Endpoints study; ISAACC, Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome;

*†Inclusion and Exclusion Criteria that are specified for PAP adherence in methodology and/or result publication and/or supplemental/appendix materials and/or publicly-availably protocol materials. ‡Reported protocol activities specific to PAP use/initiation/adherence conducted concurrent with randomization; *PAP terminology used generically to represent all forms of positive airway pressure treatment. Where trials specified type of PAP, the specified type/mode is reported; **Additional information provided by corresponding author(s).*

Abbreviations – PAP, Positive Airway Pressure; CPAP, continuous positive airway pressure; APAP, auto-adjusting positive airway pressure; Wk, Week(s); Mo, Month(s); (E), Exclusion; NR, None Reported; w/, with; min, Minute(s); PSG, Polysomnogram; q,

every; FTFV, Face-to-Face Visit(s); prn, as needed; hr, hour(s); nt, night(s); RS, Research Staff; X, times; FAQs, Frequently Asked Questions; NA, Not Applicable; CV, cardiovascular; SD, secure digital; f/u, follow-up; AHI, apnea hypopnea index; DVD, digital versatile disk; @, at; L/min, liters per minute; #, number; ETOH, alcohol.