American Thoracic Society Documents

An Official ATS/AASM/ACCP/ERS Workshop Report: Research Priorities in Ambulatory Management of Adults with Obstructive Sleep Apnea

Samuel T. Kuna, M. Safwan Badr, R. John Kimoff, Clete Kushida, Teofilo Lee-Chiong, Patrick Levy, Walter T. McNicholas, Patrick J. Strollo, Jr., on behalf of the ATS/AASM/ACCP/ERS Committee on Ambulatory Management of Adults with OSA

THIS OFFICIAL WORKSHOP REPORT OF THE AMERICAN THORACIC SOCIETY (ATS), THE AMERICAN ACADEMY OF SLEEP MEDICINE (AASM), THE AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, SEPTEMBER 2010, THE AASM BOARD OF DIRECTORS, JULY 2009, THE ACCP BOARD OF REAGENTS, OCTOBER 2009, AND THE ERS EXECUTIVE COMMITTEE, APRIL 2010

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An international workshop was held to determine the research priorities for incorporating ambulatory management of adults with obstructive sleep apnea into healthcare systems. The workshop identified the barriers preventing incorporation of portable monitor testing into clinical management pathways and determined the research and development needed to address those barriers. The workshop promoted interaction and collaboration among diverse stakeholders who have interest and expertise in the development and evaluation of portable monitor technology and its clinical application. The consensus of the workshop participants was that outcomes-based research studies are needed to demonstrate the efficacy and cost effectiveness of portable monitor testing. Closely related to this objective is the need to develop clinical sleep research networks capable of performing adequately powered studies. Recommendations were developed regarding research study design and methodology that includes the need to standardize technology, identify the patients most appropriate for ambulatory management of obstructive sleep apnea, ensure patient safety, and identify sources of research funding. The evidence resulting from high-quality comparative effectiveness studies that include cost effectiveness as an outcome will allow decision makers to develop healthcare policies regarding the clinical application of portable monitor testing for the ambulatory management of patients with obstructive sleep apnea.

Keywords: polysomnogram; apnea; hypopnea; comparative effectiveness research; cost effectiveness

EXECUTIVE SUMMARY

An international workshop was held on October 15–16, 2007 in Arlington, Virginia, to determine the research priorities for incorporating ambulatory management of adults with obstructive sleep apnea (OSA) into healthcare systems. The workshop was sponsored by the American Thoracic Society, the American Academy of Sleep Medicine, the American College of Chest Physicians, and the European Respiratory Society. Objectives of the workshop were to:

1. Identify the barriers preventing incorporation of portable monitor testing into clinical management pathways for

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the evaluation of patients with suspected OSA and determine the research and development needed to address those barriers;

2. Develop recommendations regarding research study designs and methodology that will provide needed information regarding the potential clinical application of portable monitor testing for patients with OSA;
3. Promote interaction and collaboration of representatives from government, the medical device industry, healthcare insurers, professional societies, and researchers in academic medicine who have interest and expertise in the development and evaluation of portable monitor technology and its clinical application.

Workshop participants identified the following eight interrelated research priorities for the ambulatory management of patients with OSA listed in descending order of importance:

1. Establish adequate and appropriate research networks to conduct adequately powered, multicenter clinical research studies;
2. Develop disease management models based on prospective clinical and economic outcome studies that provide evidence for clinical decision making;
3. Define the appropriate patient population for ambulatory management;
4. Standardize the portable monitor devices used to diagnose OSA and initiate continuous positive airway pressure (CPAP) treatment in terms of their sensors, signal processing, and data analysis;
5. Establish appropriate study designs that successfully address clinically relevant questions regarding ambulatory management of OSA;
6. Ensure the safety of ambulatory monitoring, especially indentifying those patient who are not candidates for this management approach;
7. Ensure adequate training and education of providers and patients regarding ambulatory management of OSA;
8. Identify funding sources to support the needed research.

Participants felt that the most important research priority is to conduct adequately powered, high quality research studies to generate the evidence needed to incorporate ambulatory management into current practice. To achieve this goal, clinical sleep research networks need to be established to evaluate ambulatory management of patients with OSA in large numbers of subjects across multiple sites. In the United States, existing practice-based research networks and the NIH Clinical Translational Research Centers may provide the essential infrastructure for such initiatives.

The advances made in portable monitor technology far outweigh our knowledge about their use in clinical testing. Approval of new portable monitor devices by the U.S. Food and Drug Administration requires their direct comparison with existing technologies. These studies should be designed to take into account the night-to-night variability in the apnea–hyponea index (AHI) on the in-lab polysomnogram and differences in equipment and testing environment. These "head-to-head" comparisons, however, do not inform us how to use the devices in clinical management pathways. Sleep testing, whether by in-lab polysomnography (PSG) or unattended home portable-monitor recording, is but one component of the clinical management pathway for patients with OSA. More prospective comparative effectiveness and economic outcome studies are needed to provide evidence for clinical decision making. Comparative effectiveness research studies need to evaluate portable-monitor testing within clinical management pathways and demonstrate the effectiveness of this management against the standard in-laboratory management in terms of clinical outcomes such as improvements in quality of life, disease-specific functional outcomes, and cardiovascular health. Investigators should incorporate economic evaluations in all such clinical trials using outcomes that are recognized benchmarks of cost effectiveness.

Anticipating that portable-monitor testing will be of greatest value in patients with a high pretest likelihood for OSA, recognition strategies that identify these high-risk patients need to be developed and validated. Future research studies should include patients with comorbid conditions, especially chronic obstructive pulmonary disease (COPD) and chronic heart failure. Patients with these prevalent conditions have been excluded from previous studies, limiting the number of potential patients who may benefit from portable monitor testing.

Despite the technological advances in portable-monitor devices, there remains a lack of standardization in terms of signals recorded, sensors, signal processing, and data analysis. Large differences can exist between monitors, even those within the same classification. Greater standardization is required. Comparative effectiveness research using different types of portable monitors may be one method to identify the optimal signals and other operating characteristics for ambulatory testing within specific patient populations.

Part of the design and evaluation of ambulatory management pathways must include careful consideration of patient safety. Although portable-monitor testing for OSA can be used as a primary diagnostic strategy, ambulatory management pathways should define the decision-making parameters for patients with negative or failed home testing who may need in-laboratory polysomnography. Ambulatory management pathways, especially those using Type 4 monitors, should also be able to identify patients with Cheyne-Stokes respiration, central sleep apnea, and complex sleep apnea. These conditions might be identified by a high AHI reported on auto-continuous positive airway pressure (CPAP) and CPAP downloads. However, the accuracy of the AHI and respiratory event information reported by positive airway pressure units still needs to be validated.

A particular challenge confronting not only future research in ambulatory monitoring but indeed the entire field of Sleep Medicine is the relatively small number of clinical investigators in this specialty. This limitation can only be exacerbated by the current Accreditation Council for Graduate Medical Education (ACGME) training requirements, which exclude a substantive research opportunity during Sleep Medicine fellowship training. Stakeholder medical specialty organizations and the ACGME urgently need to negotiate innovative solutions to optimize the feasibility and appeal of sleep clinician-scientist training pathways. As new evidence is generated about ambulatory management of OSA, its implementation will require trained healthcare providers, including sleep specialists, primary care providers, physician extenders, and allied health professionals. Training programs need to prepare healthcare providers for that future.

Finally, workshop participants recognized the importance of identifying funding sources for the needed research. The proposed research studies regarding large multicenter center comparative effectiveness will require governmental funding. Other stakeholders, including private foundations, the insurance industry, manufacturers, and the Center for Medicare and Medicaid Services should provide adjunctive resources. The high-quality outcomes-

based research conducted with this investment will demonstrate the efficacy and cost effectiveness of portable-monitor testing and generate the data needed by these funding sources for their decision making with regard to healthcare policies and directions for future research and development.

I. INTRODUCTION

An international workshop to determine the research priorities for incorporating ambulatory management of adults with obstructive sleep apnea (OSA) into healthcare systems was held on October 15–16, 2007 in Arlington, Virginia. The overall goal was to promote further research on portable-monitor testing that will generate the high-quality empirical evidence needed to determine the role of portable monitors in the ambulatory management of patients with OSA. The objectives of the workshop were to:

1. Identify the barriers preventing incorporation of portable-monitor testing into clinical management pathways for the evaluation of patients with suspected OSA and determine the research and development needed to address those barriers;
2. Develop recommendations regarding research study designs and methodology that will provide needed information regarding the potential clinical application of portable-monitor testing for patients with OSA;
3. Promote interaction and collaboration of representatives from government, the medical device industry, healthcare insurers, professional societies, and researchers in academic medicine who have interest and expertise in the development and evaluation of portable-monitor technology and its clinical application.

In addition, the workshop explored the potential resources available from the federal government, professional societies, and medical device industries to fund the research needs identified by the workshop.

The workshop was sponsored by the American Thoracic Society (ATS), the American Academy of Sleep Medicine (AASM), the American College of Chest Physicians (ACCP), and the European Respiratory Society (ERS). A conference grant awarded by the Agency for Healthcare Research and Quality (AHRQ) provided additional financial support. The workshop did not receive funding from industry. Members of the Steering Committee were selected by each sponsoring scientific society and included: M. Safwan Badr, M.D., R. John Kimoff, M.D., and Samuel T. Kuna, M.D. (Chair), representing the ATS; Teofilo L. Lee-Chiong, M.D., representing the ACCP; Clete A. Kushida, M.D., Ph.D. and Patrick J Strollo, Jr., M.D. representing the AASM; and Patrick Levy, M.D. and Walter T. McNicholas, M.D. representing the ERS. The invited workshop participants included researchers in the field of Clinical Sleep Medicine, and representatives from the American Association of Respiratory Care, medical device manufacturers, professional societies, payer organizations, and federal government agencies, including representatives of the U.S. Food and Drug Administration, the AHRQ, the Veterans Health Administration, and the National Institutes of Health. The names of the workshop participants are listed at the end of this document.

II. METHODS

The workshop consisted of four half-day sessions over the 2-day meeting period. It was structured to promote highly interactive discussions with input from all stakeholders. The initial part of each half-day session began with several short, invited presentations designed to set the framework for the session's particular theme. Participants then broke up into small groups of seven to eight individuals to discuss preidentified topics of interest. Each group consisted of a heterogeneous mix of individuals representing the different stakeholder organizations. The groups were assigned specific topics for discussion. A member of the Steering Committee was assigned to each group to organize and facilitate the discussion. In the last segment of these sessions, participants reconvened for an open discussion during which each facilitator summarized the discussions by their particular group to share ideas and develop a consensus.

Session 1

The first session focused on the technological aspects of portable monitors. Nancy Collop, M.D., from Johns Hopkins University presented the recommendations of the American Academy of Sleep Medicine's Task Force on Portable Monitor Testing that had just concluded its evaluation (1), and Conor Heneghan, Ph.D., from the School of Electronic Engineering at University College Dublin spoke about new applications of established technology. During the ensuing small-group discussions, the following topics were discussed:

1. Should portable monitors be used to both include and exclude the diagnosis of OSA, or should they be targeted to diagnose patients with a high pretest likelihood?
2. What signals are essential for the "ideal portable monitor"?
3. What if any standardization is needed of sensors, signal conditioning, and scoring?
4. Do we need more research studies on unattended auto-CPAP titration?
5. What is the best study design to validate the technical performance of portable monitors versus PSG?

Session 2

The workshop's second session identified factors that need addressing in future research to evaluate the cost effectiveness and clinical outcomes of ambulatory management pathways for patients with OSA. Henry Glick, Ph.D., from the University of Pennsylvania discussed "How to Incorporate Economic Evaluations into Clinical Trials: an Overview of Design and Analysis," and Sean Tunis, M.D., from the Center for Medical Technology Policy spoke about "Translating Emerging Technology into Clinical Practice." The following topics were discussed by the small groups:

1. Can we use PSG and portable recording as components of a disease management model to decide who receives treatment rather than relying solely on the AHI?
2. If portable monitor technology is used by nonsleep specialists, what research is needed to guide its application outside the sleep center?
3. Do we have adequate clinical prediction algorithms to assign pretest probability and, if not, how should these be developed and incorporated into diagnostic strategies?
4. For cost- and outcomes-based comparisons of in-lab versus ambulatory pathways, what are the critical outcome measures?
5. What are the best research approaches for evaluating portable monitors in diverse ethnic groups, the elderly (e.g., Medicare/Medicaid population), and among indi-

viduals with other cardio-pulmonary disease (COPD, asthma, heart failure, neuromuscular disease, etc.)?

6. What modifications of the 2003 TriSociety (AASM, ACCP, and ATS) recommendations of research studies on portable monitoring for diagnosing OSA are needed to include guidelines for outcomes-based research studies in portable-monitor testing?

Session 3

The third session of the workshop focused on identifying the research opportunities for multicenter trials in home-based chronic disease management. David Lanier, M.D., from the Center for Primary Care, Prevention, and Clinical Partnerships at the Agency for Healthcare Research and Quality spoke about "Practice-Based Research Networks." Iris Obrams, M.D., M.P.H., Ph.D., NIH Deputy Director of the Division of Clinical Research, National Center for Research Resources, spoke about "Creating Research Networks within Clinical and Translational Science Award Centers"; and Katherine Bent, R.N., Ph.D., C.N.S., from the Office of Research and Development in the Department of Veterans Affairs spoke about "Cooperative Trials and Network Opportunities in the Veterans Health Administration." This was followed by a panel discussion by experts in healthcare management on emerging portable-monitor technology: John Leteria, C.E.O. of Neurocare, Inc., Suresh Ramalingam, M.D., M.B.A., from the University of Pittsburgh, and Christopher Valerian, D.O., from the University of Medicine and Dentistry, New Jersey. During the ensuing small-group discussions, the following topics were discussed:

1. Regarding NIH-funded research of disease consequences, can portable-monitor testing without sleep staging be used as the only diagnostic sleep test in clinical trials designed to evaluate effects of CPAP treatment on hypertension and other cardiovascular outcomes?
2. Are practice-based research networks (PBRN) appropriate platforms to evaluate clinical prediction algorithms, portable-monitor testing, and outcomes on CPAP treatment?
3. Are clinical and translational research units in the U.S. appropriate platforms to evaluate clinical prediction algorithms, portable-monitor testing, and outcomes on CPAP treatment?
4. Is the replication of the Spanish Sleep Disordered Breathing Network model of a multicenter research network feasible in other countries?

Session 4

The goal of the fourth and closing session was to set priorities for future research so that "within 5 years, optimal research design(s) will generate adequately powered evidence to prove or disprove the efficacy and safety of portable monitors for the diagnosis of OSA." The Hoshin process was used to define the distant goal, elicit from stakeholders the relevant steps toward the goal, and to group, title, and stratify those steps by raw importance and as a function of prior progress (2). Using this highly interactive process, the workshop participants identified eight research priorities for the ambulatory management of patients with OSA, listed in descending order of importance in Table 1. These priorities are discussed in detail in SECTION V below.

TABLE 1. RESEARCH PRIORITIES FOR THE AMBULATORY MANAGEMENT OF PATIENTS WITH SLEEP APNEA IN DESCENDING ORDER OF IMPORTANCE

1. Establish adequate and appropriate research networks to conduct adequately powered, multicenter clinical research studies.
2. Develop disease management models based on prospective clinical and economic outcome studies that provide evidence for clinical decision making.
3. Define the appropriate patient population for ambulatory management.
4. Standardize the portable monitor devices used to diagnose OSA and initiate continuous positive airway pressure (CPAP) treatment in terms of their sensors, signal processing, and data analysis.
5. Establish appropriate study designs that successfully address clinically relevant questions regarding ambulatory management of OSA.
6. Ensure the safety of ambulatory monitoring, especially indentifying those patient who are not candidates for this management approach.
7. Ensure adequate training and education of providers and patients regarding ambulatory management of OSA.
8. Identify funding sources to support the needed research.

III. BACKGROUND ON PORTABLE-MONITOR TESTING AND SIGNIFICANCE OF THE WORKSHOP

Population-based epidemiologic studies estimate the prevalence of the obstructive sleep apnea–hypopnea syndrome (AHI of 5 events/hr with excessive daytime sleepiness) at 2% of adult females and 4% of adult males in the U.S. population. A substantial proportion of these individuals are undiagnosed (3–6). Existing evidence suggests that OSA is an independent risk factor for motor vehicle accidents, neurocognitive deficits, and cardiovascular morbidity and mortality (6, 7). Substantial evidence also supports that appropriate treatment of OSA reduces the risk of these consequences (8–11). However, the need to perform costly and labor-intensive PSG in a sleep laboratory limits patient access to diagnosis and treatment (12, 13). Commercially available and relatively inexpensive portable monitors (1, 14–16) might facilitate earlier recognition of disease and faster initiation of treatment, thereby reducing the healthcare burden associated with OSA. Interest in the clinical application of portable-monitor devices is growing rapidly and

TABLE 2. CURRENT CLASSIFICATION OF THE DIFFERENT TYPES OF SLEEP STUDIES (16)

Sleep Test	Description	Personnel	Minimum Signals Required
Type 1	Polysomnography performed in a sleep laboratory	Attended	Minimum of 7 signals, including EEG, EOG, chin EMG, ECG, airflow, respiratory effort, and oxygen saturation
Type 2	Portable polysomnography	Unattended	Same as Type 1
Type 3	Portable testing limited to sleep apnea	Attended and Unattended	Minimum of 4 signals, including ECG or heart rate, oxygen saturation, and at least 2 channels of respiratory movement, or respiratory movement and airflow
Type 4	Continuous recording of one or two signals	Unattended	Usually pulse oximetry

is being used as a mainstay approach to the management of OSA in some settings.

Numerous portable monitors for the diagnosis of OSA are commercially available. In 1994, a task force on portable-monitor testing created by the American Sleep Disorders Association (the current AASM) classified four different levels of sleep testing (Table 2) (17). Portable monitors are categorized as Types 2 to 4 based on the particular level of study they record. However, monitors within a given category may vary widely with regard to the number and type of signals recorded, the sensors used to record the signals, and signal processing.

Despite the intuitive appeal of portable-monitor testing, high-quality empiric evidence defining their role in the clinical management of patients with OSA is limited. Consequently, portable monitors have failed to gain widespread acceptance in sleep medicine. Just before the workshop, the AHRQ issued an outstanding evidence based review on portable-monitor testing (18). Subsequent to this workshop, the Center for Medicare and Medicaid Services issued two National Coverage Decisions that extended coverage for portable monitor testing to diagnose OSA and justify treatment with CPAP (19, 20). These decisions have highlighted the urgent need for research to determine the appropriate role portable monitors should play in the diagnosis and management of patients with OSA.

Current Practice Parameters to Diagnose Patients with OSA and Initiate CPAP Therapy

In-lab PSG, a recording of physiologic signals to assess sleep stage and respiration during sleep, remains the gold standard to diagnose OSA and initiate CPAP treatment (21–25). This testing is costly, uses substantial resources, and requires the supervision of a technologist. To initiate CPAP treatment, the most widely used treatment for OSA, the current standard is for an attendant technician to manually titrate CPAP during PSG to identify the optimal pressure level required for treatment. The patient is then prescribed CPAP nightly at this pressure setting. Although full-night diagnostic and manual CPAP titration polysomnograms are recommended, split-night polysomnograms (one night of testing that includes both diagnostic testing and manual CPAP titration) are frequently performed when the AHI on the initial diagnostic portion of the study is greater than 20 to 40 events per hour (21, 26). The split-night polysomnogram imposes significant time constraints on the ability to obtain the required information and has been reported to provide inadequate information regarding the prescription of the fixed pressure needed for treatment in approximately 15% of patients (27–29). Despite the drawbacks of split-night PSG, its wide use is driven by limited resources and reimbursement policies (30).

Limited In-Laboratory Resources Driving Use of Portable-Monitor Testing

The high prevalence of OSA presents major logistical difficulties for the clinical evaluation and treatment of affected patients. It is very likely that the epidemiologic data on the prevalence of OSA in the middle-aged adult in the United States population from the Wisconsin Sleep Cohort Study published in 1993 underestimates the current prevalence of OSA in the U.S. population given the dramatic increase in obesity over the past 20 years (5, 31). Nevertheless, applying the findings in middle-aged adults from the Wisconsin Sleep Cohort Study, that 9% of males and 4% of females in the U.S. have moderate to severe OSA (AHI of at least 15 events/hr), Tachibana and colleagues (32) estimated that 2,310 sleep studies per year per 100,000 population would be required to adequately address the demand for diagnosis and treatment of patients with suspected OSA of at least moderate severity. The capacity for sleep testing is inadequate to meet even those conservative demands. Specifically, the total number of sleep laboratories in 2002 was about 1,300 in the private sector and 55 in the Veterans Health Administration. These laboratories had the capacity to perform approximately 430 studies per year per 100,000 population and 160 studies per year per 100,000 population, respectively. These limited and costly resources restrict patient access to testing and are driving the need for alternative management strategies using portable-monitor testing. Indeed, portable-monitor testing is increasingly used by healthcare providers, particularly those working in capitated and public healthcare systems (12). In 2005, an editorial on international clinical practices for the diagnosis of patients with OSA commented that

> Faced with the dilemma of how to treat the "flood" of patients presenting with symptoms suggestive of sleep-disordered breathing, physicians are using nonconventional approaches for diagnosis and treatment—approaches not based on solid evidence. Most surprising ... is the widespread use of ambulatory approaches to diagnosis rather than full in-laboratory polysomnography. With the increased recognition of OSA, systems for delivering diagnosis and treatment are overwhelmed. Physicians are trying to cope but, even with creative approaches, waiting lists for diagnosis and treatment are unacceptably long. There is a need to rethink current strategies. (13)

IV. HEALTHCARE MANAGEMENT AND INSURANCE-INDUSTRY PANEL PERSPECTIVE ON EMERGING PORTABLE-MONITOR TECHNOLOGY

A panel discussion was held during the workshop to learn how healthcare management and the insurance industry evaluate emerging technologies. The panel included John Leteria, CEO of Neurocare, Inc., Suresh Ramalingam, M.D., MBA from the University of Pittsburgh, and Christopher Valerian, DO from the UMD of New Jersey. The panel addressed four questions:

1. What criteria should be used by healthcare management and the insurance industry to evaluate acceptance of an emerging technology into clinical practice?
2. What type of evidence is needed to support the evaluation of portable monitor testing?
3. In the absence high-quality evidence, what would be the best way to assess portable monitoring as part of a disease-management pathway?
4. Once portable monitoring is incorporated into a disease-management pathway, how can providers be assured that in-lab PSG can be performed when indicated?

The criteria used by healthcare management and the insurance industry to evaluate acceptance of an emerging technology into clinical practice include data from peer-reviewed studies, evidence-based reviews (Cochrane, etc.), industry reports, and other studies demonstrating safety and efficacy. The Food and Drug Administration trial results and approval are also essential. National guidelines and regulatory directives and community standards are also considered. Other factors in decision making include whether quality-control criteria are present and whether a certification process is required for those who will deliver the service. The potential for misuse or abuse is also a consideration. Notably, cost-benefit analysis becomes a primary incentive for payors once safety and efficacy issues have been adequately addressed.

These principles apply to the evaluation of portable-monitor testing. High-level supporting evidence would be ideal, but in its absence, other available data should be used to formulate policy until high-level research data are available. The recent Center for Medicare and Medicaid Services (CMS) National Coverage Decisions to accept portable-monitor testing for the diagnosis and coverage of CPAP treatment and the application of these decisions by local carriers is likely to strongly influence payors. However, more careful analysis of how portable monitoring will impact patient access, compliance, and outcomes, is needed. Cost-benefit analysis must go far beyond the relative costs of portable monitoring versus in-lab PSG. An intent-to-treat analysis of clinical outcomes for each treatment option is critical to this assessment. Patient adherence to CPAP following ambulatory and in-lab testing should also be compared in a secondary per-protocol analysis. One must factor in the associated after-study costs of patients positively diagnosed with OSA. All costs associated with the continuum of care (CPAP equipment and disposables, dental appliance or surgical intervention, physician visits, etc.) must be taken into account.

As a primary diagnostic technique, ambulatory testing of patients with OSA will improve access to testing but will require that patients being evaluated have access to a sleep center when the portable-monitor testing is unsuccessful or not feasible due to medical, social, and logistic reasons. Therefore, payor policy should recognize and accommodate in-lab PSG at the discretion of the physician and subject to patient choice. There should be specified guidelines for choosing a portable or in-laboratory study as the first test, as well as clear definitions for failure of portable monitoring requiring subsequent in-lab PSG. Review of clinical practice data should indicate that redundant testing in the lab is done rarely, and if this is not the case, policies and procedures should be modified.

Overall, the discussion by the panel members served to underscore the importance of high-quality, outcomes-based research for guiding decision making by health management and insurance industries on ambulatory monitors in the management of OSA.

V. WORKSHOP FINDINGS AND RECOMMENDATIONS

The following eight key research priorities identified by the Workshop for the ambulatory management of patients with OSA are presented in descending order of importance (Table 1).

1. Establish Adequate and Appropriate Research Networks to Conduct Adequately Powered, Multicenter Clinical Research Studies

Existing multicenter studies and research networks for OSA. The optimal approach for assessment and management of patients with OSA in the ambulatory setting remains uncertain. Although specific technical questions are amenable to testing in a single specialized center, the development and evaluation of clinical management strategies and outcomes based on portable-monitor testing require patient populations that are too large for single center studies. The sleep research community needs to follow the approach of other specialties, such as cardiology, that conduct multicenter studies to evaluate particular clinical interventions in large numbers of patients.

Some notable multicenter research collaborations have been established in recent years to investigate the epidemiology, comorbidities and therapeutic outcomes of OSA. In North America, these include the NIH-funded Sleep Heart Health Study, that particularly addressed the cardiovascular comorbidities of the disorder, and the Canadian Medical Research Council funded CANPAP (Canadian Positive Airway Pressure) clinical trial that evaluated the potential role of nocturnal CPAP therapy in patients with chronic heart failure (33, 34). In Europe, a number of multicenter studies relating to OSA are ongoing such as the MOSAIC (Multicenter Obstructive Sleep Apnoea Interventional Cardiovascular Trial) study of mild OSA, based in the UK, and the ESADA (European Sleep Apnea Database) study of cardiovascular disease in OSA, which includes more than 20 sleep centers throughout Europe. The ESADA project is part of a collaborative network of sleep centers throughout Europe, funded by the European Union as part of the COST Action scheme (http://www.costb26.net/). The above initiatives are best described as extended multicenter studies established to examine particular research topics. However, the ESADA study involves the establishment of a common European database of patients with OSA using standardized and uniform inclusion criteria and has the potential to expand into a research network.

The Spanish Sleep Disordered Breathing Network is an excellent model of a multicenter network that has made important scientific contributions relating to the study of OSA. This network consists of a number of sleep centers throughout Spain and was established to allow the collaborative study of a variety of topics relating to OSA, ranging from epidemiology to disease management. A number of important principles underpin the success of this network. First, the network was developed as collaboration among equals and adopts a democratic, nonbureaucratic approach. Second, each specific study undertaken by the network members has one of the collaborators identified as the principal investigator and who is thus responsible for the successful implementation of the protocol. Third, the network members interact regularly to monitor ongoing activities and to identify new topics for investigation.

A number of existing networks and programs in the United States could facilitate the implementation of large-scale collaborative sleep research projects. These include the Primary Care Practice-Based Research Networks (PBRN), the Clinical and Translational Research Centers (CTRC), and networks within the Veterans Health Administration (VHA). PBRNs involve groups of ambulatory care practices throughout the U.S. that collaborate to investigate clinical questions applicable to primary care. Such networks typically operate under the auspices of a professional or academic organization and usually depend on outside funding to support research activities. PBRNs have the advantage of being able to evaluate clinical decision making and provision of services to a large number of individuals in a primary care setting. The CTRCs are funded by a NIH clinical research program to promote collaboration between and within academic centers of excellence. The program is intended to provide relatively large-scale funding to a small number of academic health centers and support a range of activities including protocol development and implementation, education, and collaboration between clinical and basic researchers. The CTRC infrastructure provides an opportunity for sleep centers located in these institutions to build a clinical sleep research network. Finally, the VHA operates three collaborative research programs that could potentially serve as funding and infrastructure platforms for portable monitor research: PBRNs, the Cooperative Studies Program (CSP), and the Health Services Research and Development (HSRD) program. These programs have the advantage of operating within a uniformly structured national healthcare network that includes specialized sleep centers.

Priority 1: Establish adequate and appropriate research networks to conduct adequately powered, multicenter clinical research studies. Essential components for an effective research network:

- A robust organizational structure consisting of a designated leader and a steering committee is critical for the initial set-up of the network and in driving the research program forward;
- A broad participation of sleep research centers with appropriate facilities and expertise to implement the envisaged research program;
- An infrastructure capable of supporting and monitoring the planned research;
- Effective communication between all interested parties in the process including manufacturers, third party payers, professional bodies, and the public;
- Effective mechanisms for national/global tracking of progress in portable monitor research.

2. Develop Disease Management Models Based on Successful Clinical and Economic Outcomes

Clinical outcome-based measures for comparing in-lab versus ambulatory pathways. Recent evidence reviews have highlighted the need for a focus on outcomes-based studies involving ambulatory monitors. It is important to assess the performance characteristics of specific monitors in the intended clinical context and patient population. However, studies should not simply assess the ability of the monitor to reproduce a PSG-derived AHI. Instead, it is imperative to perform comparative effectiveness research studies that ascertain the clinical outcomes of OSA management pathways using portable-monitor testing versus in-laboratory testing. The workshop participants strongly endorsed this principle for future studies of portable monitors.

Study designs evaluating ambulatory management strategies should take into account that differences in the modality of testing may influence a patient's attitudes and perceptions about OSA and thereby influence their subsequent adherence to CPAP treatment. Differences between testing methods might arise due to the greater amount of time healthcare providers interact with patients during in-laboratory versus home testing (35). Increased opportunities for patient education and support have been shown to improve patient adherence to treatment (36, 37). Administering a self-efficacy questionnaire at several time points throughout the protocol may help assess the impact of specific interventions (38–40).

The clinical and cost-related outcomes in comparative effectiveness research studies must be carefully selected and clearly defined. Ideally, both short-term and long-term outcomes should be evaluated. Workshop participants identified the need to develop a consensus on the most appropriate outcome measures and to standardize these for use in research studies. Pending such a consensus, there are categories of validated outcome measures that should be incorporated into study protocols. These categories include general and disease-specific quality of life measures, sleep-related symptoms, and objective measures of neurocognitive function. Examples of functional outcome measures include: the Psychomotor Vigilance Task (PVT) for objective assessment of daytime sleepiness, the Epworth Sleepiness Scale (ESS) for subjective assessment of daytime sleepiness, disease-specific quality of life questionnaires such as the Functional Outcomes of Sleep Questionnaire (FOSQ) and the Calgary Sleep Apnea Quality of Life Index (SAQLI), and general quality of life questionnaires such as the Short Form-36 and Short Form-12 (41–49).

Cardiovascular outcome measures should also be clearly defined in study protocols. These may include direct measures of cardiovascular function (individual or 24-hr blood pressure measurements, ECG measurements including rhythm and ischemic changes, and echocardiographic changes) or documentation of clinical cardiovascular events (ischemic, heart failure, transient ischemic attack, or stroke). Surrogate measures of cardiovascular risk (e.g., circulating or tissue biomarkers, measures of endothelial function, and vascular intimamedia thickness) and assessment of metabolic function (lipid metabolism and insulin resistance) may also be relevant. Ideally, studies should seek to identify the impact of portable monitors on long-term cardiovascular morbidity and mortality. The challenge in designing randomized studies with hard cardiovascular outcomes, however, is that of including an ethically acceptable control group and thereby overcome the problems inherent in observational study designs (50).

The workshop did not endorse any specific study design for future comparative effectiveness research. Participants did discuss two ongoing research projects evaluating the ambulatory management of OSA that have similar study designs (Figure 1). The Veterans Health Administration is funding one of the studies, and the other is funded by the American Sleep Medicine Foundation. In both protocols, patients with suspected OSA were randomized to standard in-laboratory testing versus overnight home unattended testing with a Type 3 portable monitor. Those participants testing positive for OSA on the home recording performed a home-unattended autoCPAP titration study for several nights. Patients diagnosed with OSA in both arms were initiated on CPAP treatment and reassessed after 3 months of treatment.

Comparative effectiveness research studies must take into consideration that different testing modalities (portable-monitor testing vs. PSG) are being used to diagnose OSA. For example, AHI on the baseline sleep study should not be used to determine whether participants randomized to each arm have a similar severity of OSA insofar as the portable-monitor study (without sleep staging) tends to underestimate the AHI that would be obtained with PSG. Another indicator of disease severity, such as the Multivariable Apnea Prediction Index (51, 52), could be used to assess disease severity at baseline across the two groups. Studies can attempt to compensate for these differences in diagnostic accuracy by performing polysomnography in those patients with negative home studies. This approach, however, is also potentially problematic. The option of a second diagnostic test in the home group and not the in-lab group may make it more likely, due to night-to-night variability in AHI, that the diagnosis of OSA will be established in patients randomized to home testing.

To compare the two management pathways using an intent-to-treat analysis, these comparative effectiveness research studies should select a primary outcome that evaluates all participants randomized to each arm of the study, regardless of whether or not they were diagnosed with OSA and initiated on CPAP treatment. CPAP adherence should not be the primary outcome measure since different percentages of participants randomized to each arm may be diagnosed with OSA and treated with CPAP. CPAP adherence is an outcome of interest but is limited to a per protocol analysis.

Cost effectiveness. During the workshop, there was considerable discussion on the importance of evaluating the cost

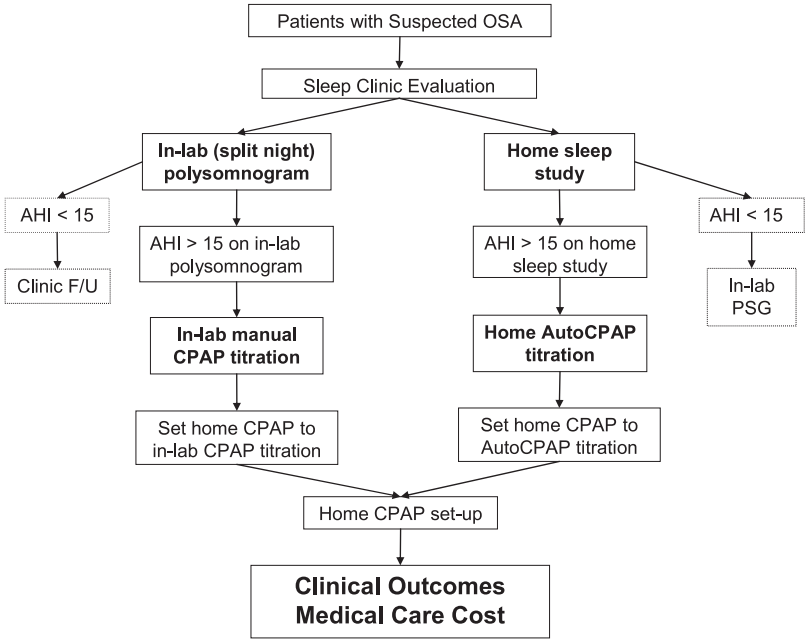

Figure 1. Alternative clinical management pathways for patients with obstructive sleep apnea (OSA). The pathway on the left represents the standard in-laboratory management and the pathway on the right represents a possible approach using home-unattended portable-monitor testing. PSG, polysomnogram; CPAP, continuous positive airway pressure.

effectiveness of portable monitors. Henry Glick, Ph.D. addressed the topic "How to incorporate economic evaluations into clinical trials: an overview of design and analysis." (53) Economic data collected as primary or secondary endpoints in randomized trials are commonly used to evaluate whether there is "good value for the cost" of medical therapies. Short-term economic impacts are directly observed in studies, while longer term impacts can be projected by the use of decision analysis. The key steps in economic evaluation are to: (*1*) quantify the costs of care, (*2*) quantify outcomes, (*3*) assess whether and by how much average costs and outcomes differ among the treatment groups, (*4*) compare the magnitude of difference in costs and outcomes and evaluate "value for costs" (e.g., by reporting a cost-effectiveness ratio or the probability that the ratio is acceptable), and (*5*) perform sensitivity analyses.

Economic analyses should evaluate health resource use for the entire clinical management pathway, from diagnosis to treatment outcomes. Ideally, economic evaluation within a trial should measure all costs of all participants before randomization and for the duration of follow-up. The costs after randomization represent the cost outcome, whereas the costs before randomization are a potential predictor of outcomes. Four strategic study design issues for cost analysis were addressed:

1. What medical service use should one collect?
2. How naturalistic should the study design be?
3. What is the appropriate sample size?
4. What is the likelihood that the cost-effectiveness ratio observed in the trial describes longer-term therapy?

Study-specific costs to consider include: sensor/supply and equipment purchases; maintenance and refurbishment/replacement due to damage from portable use and/or theft; laboratory space; and personnel costs, including staff training/development as well as workload for equipment management, patient training, data download, and scoring. Other costs arise from failed or inconclusive studies that need to be repeated, or for which PSG eventually has to be performed; the costs associated with incorrect or missed diagnosis of sleep-disordered breathing; failure to diagnose concomitant nonrespiratory sleep disorders, and treatment failures, such as nonacceptance of CPAP.

Several economic analyses of ambulatory management of patients with OSA have been reported (54–58). Three of the studies were based on decision analysis, and their impact is diminished because the inputs used for modeling analysis were not based on direct observation (55, 56, 58). Two studies assumed unacceptably high failure rates for home testing (57, 58). There has been only one prospective economic evaluation of portable-monitor testing (54). Using the change in the total score on the Epworth Sleepiness Scale questionnaire (44) to assess functional outcome, this study found that a nurse practitioner–led management of patients with OSA using portable-monitor testing was more cost effective than physician-led management using in-laboratory PSG (54). More prospective randomized controlled trials on cost effectiveness are needed to collect evidence under naturalized, realistic conditions that can be used for a modeling analysis. These data can then be used to perform decision modeling that will help sleep specialists decide whether to use the more expedient home testing versus accepting delays in obtaining in-lab testing. Modeling on these data can also determine the utility of home testing in patient populations with different prevalence of OSA. Only one study has addressed whether it is better to use home testing sooner or whether it is better to wait for in-laboratory testing (59). That study reported that earlier diagnosis and treatment was cost effective compared with waiting.

What medical-service use should one collect? To assess the cost impact of a therapy, one should be sure to determine the use of services arising from differences in treatment between the arms of the study. It is also important to measure high-cost services. Minimizing the number of unmeasured services reduces the likelihood that differences among them will lead to biased estimates. In fact, it is prudent to capture as many services as possible. The general strategy should be to identify a set of pertinent medical services and assess their utilization longitudinally, independent of the reason for their use. There are no *a priori* guidelines about how much data are enough, nor

are there data on the incremental value of specific items in the economic case-report form. One should consider collecting costs other than medical service use that may be of use to medical decision makers, such as time costs (e.g., lost time due to illness and treatment). Practically, decisions about the services to measure should take into account the expense of collecting particular data items.

During trial design, it is important to document potential service use. Decisions are improved if there is documentation of the types of services used by patients who are similar to those who will be enrolled in the trial. This can be achieved through medical record review, administrative data sets, surveys of patients and experts about the kinds of care received, or through patient logs of their healthcare resource use. One should also evaluate the possibility that a new therapy will induce different medical service use.

How naturalistic should the study design be? The primary purpose of cost-effectiveness analysis is to inform real-world decision-makers how to respond to real-world healthcare needs. Thus, the more naturalistic the trial—in terms of participants, analysis based on the intention to treat, and limitation of loss to follow-up—the more likely the data developed within the trial will speak directly to the decision question.

While advocating a naturalistic framework to assess cost effectiveness, the workshop participants also cited important elements that should be included in studies. Treatment efficacy and patient satisfaction with the care path should be considered. Relative wait times, and the number of lost, technically unsatisfactory, and/or equivocal studies should be recorded, together with the criteria for each of these categories. Objective measures of treatment response should include the change in AHI/respiratory disturbance index (RDI), oxygenation and, when available, changes in measures of sleep structure. Objective adherence to CPAP treatment is an essential outcome measure, and the software and thresholds used to determine adequate adherence need to be clearly specified.

The design of clinical trials should include plans for robust follow-up of participants to minimize missing data due to the loss to follow-up. It is also important to continue data collection and follow-up until the end of the study period and not discontinue data collection because a subject reaches a clinical or treatment stage such as failure to respond. Given that failure is often associated with a change in the pattern of costs, discontinuation of these patients from the study is likely to bias the results of an economic evaluation that is conducted as part of the trial.

Trial-based cost-effectiveness analyses should adopt an intent-to-treat design. Economic questions relate to treatment decisions (e.g., whether to prescribe a therapy) and not to whether the patient received the prescribed intervention, such as CPAP, nor to whether, once they started the prescribed intervention, they were switched to another treatment option. Thus, costs and effects associated with these later decisions should be attributed to the initial treatment decision.

What is the appropriate sample size to address economic questions? Economic sample size calculations are based on the number of study subjects needed to rule out that the therapy is unacceptable (equivalently, to ruling out that the net monetary benefits of the intervention are less than 0). Key factors in sample size formulae include numbers of subjects, the standard deviation for costs and treatment effects, the maximum willingness to pay that one wishes to rule out, and the correlation of the difference in cost and effect. The required sample size is less when the therapies have a Win/Lose (positive) correlation (i.e., as the effectiveness increases, the cost increases, e.g., stroke care). The required sample size is greater when the therapies have a Win/Win (negative) correlation (i.e., as the effectiveness increases, the cost decreases, e.g., asthma care). With respect to maximum willingness to pay and identification of an appropriate outcome measure, the sample size calculations assume that there is some concept of what one would be willing to pay to obtain a unit of outcome. Many researchers use disease specific outcomes. Although any outcome can be used to calculate a cost-effectiveness ratio (e.g., cost/case detected or cost/additional abstinence day), the outcome must have recognized benchmarks of cost effectiveness to be convincing that a new, more costly and more effective therapy has good value. This argues against the use of too disease-specific an outcome for economic assessment.

If portable monitor testing is both clinically equivalent to and less expensive than in-laboratory testing, a "disease-specific" outcome such as cases detected may be sufficient (depending on "how equivalent" it is). If home testing is less effective and less expensive, one needs to know the value of the lost effectiveness so that it can be compared with the cost savings. This requires that we either know the worth of detecting a case or use a more general health outcome such as quality adjusted life years (QALYs). OSA research is at a disadvantage because the cost effectiveness of diagnosis of OSA has not been well established experimentally.

What is the likelihood that the cost-effectiveness ratio observed in the trial describes longer-term therapy? A time-by-treatment interaction manifests when cost and outcome follow different time courses. For example, risk reduction from cholesterol-modifying therapy displays substantial time-by-treatment interaction given the lag time between initiation of therapy and improved outcome. Conversely, drug therapy for heart failure displays less interaction as the treatment and outcome are incurred together. If a strong treatment-by-time interaction is expected, a decision model will be required to ascertain the potential magnitude of the interaction. Substantial amounts of the data used for the decision model should be derived from the trial and, when necessary, augmented with data from epidemiological studies.

In summary, clinical trials are invaluable opportunities for evaluating the cost effectiveness of a therapy. If complete data sets are collected and analyzed appropriately, these evaluations can provide data about uncertainties related to the assessment of the value for the cost of new therapies that may be used by policy makers, manufacturers, healthcare providers and patients when the therapy is introduced in the market.

Priority 2: Develop disease management models based on successful clinical and economic outcomes. Recommendations:

- Develop and validate recognition strategies to identify patients with high pretest likelihood of OSA;
- Incorporate ambulatory monitors into disease management pathways evaluating clearly specified OSA-related outcomes;
- Develop consensus on the most appropriate outcome measures and standardize their use in research studies;
- Include economic evaluations in clinical trials using outcomes that are recognized benchmarks of cost effectiveness;
- Generate data from high quality studies that can be used to develop decision analytic models.

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3. Define the Appropriate Patient Population for Ambulatory Management

Establishing the optimal role of portable sleep monitors. Another goal of the workshop was to promote research to determine the role portable monitor testing should play in the diagnostic evaluation and management of patients with OSA. Debate continues as to whether portable monitor testing should be used diagnostically in the general population or in a subgroup such as diagnosing patients with a high pretest likelihood of the disorder. In most current clinical applications, Type 3 portable monitors (monitors that record respiratory-related signals but do not record the PSG signals for sleep staging) are used for unattended home recordings to diagnose OSA. It is recommended that those patients with a negative Type 3 recording have an in-laboratory PSG to exclude the possibility of a false negative study (1). Using portable monitors to include and exclude the diagnosis of OSA in the general population would result in a greater proportion of negative studies increasing the demand for in-laboratory PSG. Limiting portable monitor testing to patients with a high-likelihood of OSA would minimize the number of negative studies and the need for in-laboratory PSG. Therefore, accurate identification of patients with a high pretest likelihood of OSA is essential. Clinical prediction rules, including the Multivariable Apnea Prediction Index, Sleep Apnea Clinical Score, and Berlin Questionnaire, have been used for this purpose in research studies but they have not been adequately tested in clinical management pathways (51, 52, 60, 61).

Study populations that need to be included in portable monitor research. Very few published studies have assessed portable monitors in specific populations, including diverse ethnic groups, the elderly, and individuals with cardio-respiratory and neurological diseases. Participants at the workshop discussed the best research approaches for evaluating portable monitors in these subgroups.

The initial question that needs to be addressed is whether portable monitor testing is feasible and suitable for the screening and diagnosis of OSA in technologically challenged, socially disadvantaged, and medically disabled populations. Are there any specific sensors that are more suitable for certain subpopulations? Should diagnostic and/or therapeutic threshold values for respiratory disturbance indices differ between populations? How would portable-monitor testing, compared with PSG, affect response and adherence to positive airway pressure therapy? What is the likelihood of repeat testing due to inadequate or suboptimal data collection with portable monitor testing or PSG in the different study populations?

Research is needed on adapting portable monitors to patients with specific comorbid medical and neurological conditions. Persons with COPD, asthma, heart failure, and neuromuscular disorders have a higher risk of developing sleep-related hypoventilation and central sleep apnea. Ideally, portable-monitor testing in these patients should be able to distinguish these respiratory disorders. Appropriate sensors and bioparameters (e.g., oxygen saturation, airflow limitation, respiratory effort) for each condition need to be defined.

Any study evaluating portable monitors should include a diversity of racial and ethnic groups. The impact of differing languages and cultures on portable monitor testing should be assessed by engaging existing social and medical networks working with different ethnic groups. Among the elderly population, many of whom have multiple comorbid conditions (e.g., medical or other primary sleep disorders such as periodic limb movement disorder), it is important to identify the factors that influence the performance of sleep studies using portable monitors, and develop management pathways that ensure patient safety during the testing. Use of telemetric monitoring might be explored as one such approach. Studies on the relative feasibility, access, and convenience of the portable monitor compared with in-laboratory PSG among community-dwelling compared with nursing home adults are also important.

In summary, the participants of the workshop identified several research priorities related to the study population, including a focus on high-risk subjects with cardio-pulmonary and neurological comorbidities, older adults, and persons with different ethnic groups. Appropriate outcome measures for each study population will need to be identified.

Priority 3. Define the patient population most appropriate for ambulatory management. Recommendations:

- Target groups not previously studied to identify those best suited for portable testing;
- Identify and report the age, sex, and ethnic characteristics of the study population, as well as the nature and severity of any underlying cardiopulmonary disease or other comorbid condition;
- Consider the characteristics of the study population in all aspects of study design and analysis.

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4. Standardize the Portable Monitor Devices Used to Diagnose OSA and Initiate Continuous Positive Airway Pressure (CPAP) Treatment

Current lack of standardization among portable monitors. The current lack of standardization of commercially available monitors is a major barrier preventing the incorporation of portable-monitor testing into routine clinical management pathways. Although portable monitors for sleep testing are intended primarily for unattended home recordings, they can be used under attended or unattended conditions and in a variety of locations, including the sleep laboratory and healthcare facilities. The monitors differ widely in the number and type of signals recorded, the sensors used to record the signals, and the electronic processing of the signals. Scoring of the recordings may be totally automated or manual with the assistance of computer software

As stated in a recent practice parameter report on portable monitor testing, "There is no universally accepted platform for generating simplified studies in the diagnosis of OSA. This means that results obtained for a particular device are applicable to that device and cannot be extrapolated to other devices, even those of the same class" (62). This lack of uniformity limits the impact of evidence-based reviews that evaluate the results of research studies performed using monitors within a particular category without consideration of the technological differences that exist among these monitors. Although further standardization of portable monitors is needed, important technological questions remain to be answered before we can determine the ideal portable monitor for diagnosis of OSA. We still need to determine which signals are essential and how they should be acquired in terms of sensors used, sampling rate, and filtering.

Innovative signals and approaches to portable monitor testing. In addition to the standard PSG techniques that have been adopted for portable monitor testing, novel technologies have been developed to enhance their performance and application (63). For example, actigraphy has been evaluated as a surrogate marker of sleep and wakefulness to improve the

calculation of AHI (64). In one commercially available Type 3 monitor, the sensors that record nasal pressure, oximetry, head movement, snoring, and respiratory effort (venous pulsations) are contained in a headband worn around the forehead (65). Some monitors incorporate other novel sensors that detect cardiac and autonomic responses to sleep-disordered breathing. One such device measures peripheral artery tone from a sensor on the finger that estimates changes in vascular flow, a measure that reflects variations in breathing and sleep-related arousals (66). Unfortunately, the advances made in portable monitor technology far outstrip our knowledge about their utility in clinical testing. This wide diversity in portable monitors complicates the ability to compare results across monitors and to generalize results obtained with a particular monitor. The test for any instrumentation is its role in clinical decision making. This being the case, it is important to standardize a core set of features so that one can compare one to another and then show the effects on clinical decisions.

Issues regarding signal acquisition. The central premise of portable monitors is that a few signals, extracted from PSG, are necessary and sufficient for the diagnosis of OSA. An ideal portable monitor should provide sufficient accuracy for case finding, should be amenable for self-application, comfortable for all-night use, and durable enough to withstand nightly transport and application in the home by inexperienced patients. Moreover, the monitors should provide full disclosure of high-quality primary signals for manual review and either manual scoring or manual editing of automated scoring. In addition, the device should provide computational algorithms, allowing them to be used in a large number of patients. In other words, an ideal portable monitor should contain high-quality primary signals without requiring excessive labor and perhaps redundancy of signals to provide complementary data acquisition and minimize data loss. In addition, there is an unmet need to ascertain the variables that predict long-term outcomes in OSA. Longitudinal data linking specific physiologic signals to neuro-cognitive consequences, daytime hypersomnolence, or adverse cardiovascular outcomes, are needed. Furthermore, different variables may predict different outcomes.

Several questions await further evidence to ascertain primary signals for portable monitoring.

1. What is the cost of repeated studies resulting from failed data acquisition versus the cost of technical time required for full PSG?
2. Should the design of portable monitors allow for the application of the sensors by the patient?
3. What are the limitations of acquired signals under various clinical settings? For example, noninvasive determination of respiratory effort using respiratory inductance plethysmography is more likely to capture paradoxical breathing in children with a compliant chest wall than in a morbidly obese individual with reduced chest-wall movement.
4. Does the usefulness of individual signals vary by the population being tested? For example, oxyhemoglobin desaturation is more likely to occur in obese rather than thin individuals.

Standardizing sensors, signal conditioning, and scoring. The ideal sensors should be easy to apply and capable of providing a core group of reliable signals. The output of sensors should be accurate, reliable, and reproducible. Oximetry, flow using nasal pressure, ECG, and respiratory effort are the primary signals requiring standardization and validation. In contrast, sleep staging is less critical in portable-monitor testing. Accurate diagnosis also requires scoring standards to minimize variability. Current AASM PSG scoring standards are applicable to portable recordings and may be amenable to autoscoring. Given the limitations of current technology in terms of lack of standardization, variability between devices, and differences in software interpretation, it seems logical to first resolve these problems. One possible approach would be to conduct multicenter comparative effectiveness studies to compare different portable monitors against each other and evaluate their performance in terms of clinical outcomes.

Priority 4. Standardize the portable monitor devices used to diagnose OSA and initiate continuous positive airway pressure (CPAP) treatment. Recommendations:

- Standardize equipment and specific signals;
- Standardize therapeutic devices and their outputs;
- Identify the minimal and ideal signals and their biosensors;
- Compare Type 3 to Type 4 portable-monitoring devices;
- Develop a common interpretive taxonomy and data platform for portable-monitoring devices.

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5. Establish Appropriate Study Designs That Successfully Address Clinically Relevant Questions Regarding Ambulatory Management of OSA

Closely related to the need to develop disease-management models based on successful clinical and economic outcomes (Priority 2) is the need to design studies that successfully evaluate the effectiveness of those models.

Limitations of validation studies directly comparing portable monitor testing and PSG. Differences in equipment and testing environments, intrascorer reliability, and the known night-to-night variability in AHI may explain why direct comparisons of results from portable monitor testing and PSG are not closely correlated. Most portable monitors capable of widespread application do not include signals that detect whether the patient is awake or asleep during the recording. The severity of the sleep-disordered breathing on these recordings is therefore quantified as the number of apneas and hypopneas per hour of recording, instead of the number per hour of sleep, and is sometimes referred to as the respiratory disturbance index (RDI) rather than the AHI. In patients with delayed sleep onset and low sleep efficiency, the resulting AHI will underestimate the "true" AHI. Although the correlation between in-laboratory PSG and Type 3 monitor testing is generally acceptable when the recordings are performed simultaneously in the sleep laboratory, all evidence-based reviews comment on the importance of validating portable monitors in the home environment, the intended location for their use.

Validating Type 3 portable monitors based on clinical outcomes. Recognizing the limitations of studies that directly compare sleep test results between portable monitors and in-laboratory PSG, investigators are starting to perform studies that compare participants randomized to these different pathways in terms of improvements in quality of life and other clinical outcomes. Assuming that PSG has a higher sensitivity than portable-monitor testing, patients randomized to home testing may not be diagnosed with OSA on the portable-monitor recording, whereas they would have been diagnosed on PSG. The resulting inequality between groups might influence the

results of outcome measure(s) such as adherence to CPAP treatment. Studies can attempt to compensate for these differences in diagnostic accuracy by performing PSG in those patients with negative home studies. This approach, however, may also influence study outcomes. The option of a second diagnostic test in the home group and not the in-lab group makes it more likely, due to night-to-night variability in AHI, that the diagnosis of OSA will be established in patients randomized to home testing.

Priority 5: Establish appropriate study designs that successfully address clinically relevant questions regarding ambulatory management of OSA. Recommendations:

- Research studies to validate performance of portable monitor equipment against PSG should be designed to take into account the night-to-night variability in AHI on the in-lab polysomnogram and differences in equipment and testing environment.
- Research studies on portable monitor testing should evaluate the outcomes of integrated ambulatory management pathways as well the key components of those pathways (e.g., diagnostic, therapeutic strategies)
- The role of autoCPAP units in the management of patients with sleep apnea and the cost effectiveness of ambulatory pathways needs further investigation.

Use of autoCPAP to titrate the pressure setting needed for CPAP treatment. The current AASM practice parameter for portable monitor testing recommends that a manual CPAP PSG be performed in patients with a positive Type 3 diagnostic study (62). However, the use of home-unattended portable-monitor testing to diagnose patients with OSA apnea will only alleviate the growing demand for in-laboratory testing if those patients can be initiated on CPAP treatment without requiring PSG to establish the optimal CPAP setting. AutoCPAP units have been used successfully to titrate the fixed pressure setting needed for CPAP treatment in attended and unattended settings (54, 67, 68). Increasingly, providers are using autoCPAP instead of CPAP for regular treatment. However, no consensus exists regarding the optimal role of autoCPAP machines in the clinical management of patients with OSA. One of the important barriers to the acceptance of portable-monitor testing for OSA in the United States is the lack of benefit coverage for home-unattended autoCPAP titration studies.

6. Ensure the Safety of Ambulatory Monitoring, Especially Identifying Those Patients Who Are Not Candidates for This Management Approach

Discussion about safety issues regarding portable-monitor testing related primarily to the appropriate validation of the devices with respect to diagnostic accuracy in relevant populations, and the responsible application of diagnostic information from the monitors to patient management. It was felt that portable-monitor units that distinguish obstructive and central apneas will have wider application; whereas units lacking this capability will require validated clinical correlation to exclude patients with central sleep apnea.

AutoCPAP features that help ensure patient safety. To prevent adverse events related to excessive pressure, the autoCPAP machines are limited to a pressure range from 4 to approximately 20 cm H_2O. AutoCPAPs are unable to distinguish central from obstructive apneas. Therefore, to avoid the potential problem of increasing pressure in the presence of central apneas, autoCPAP algorithms uniformly prevent increases in pressure greater than 10–11 cm H_2O in the presence of persistent apneas. Data uploaded from autoCPAP units report not only the pressures delivered but also the AHI, number of apneas, and amount of air leak. Studies are needed to document the accuracy of these measurements.

To ascertain the effectiveness of autoCPAP treatment in restoring oxygen saturation to acceptable levels, some autoCPAP devices can interface with pulse oximeter modules to record oxygen saturation and heart rate. Some autoCPAPs are also designed to interface with a portable monitor for a verifiable documentation of AHI as well as oxygen saturation. The latest innovations in autoCPAP machines allow remote monitoring of their use and performance either by modem or wireless transmission of recorded data. Although no studies have investigated the use of this innovative technology, the ability to remotely track events during the home titration may enable early intervention that can promote successful titration and initiation of CPAP treatment.

Priority 6. Ensure the safety of ambulatory monitoring, especially indentifying those patients who are not candidates for this management approach. Recommendations:

- Develop validated clinical management pathways using portable monitor testing that define the decision making parameters that result in accurate diagnosis andtreatment of OSA;
- Develop ambulatory management pathways, especially those using Type 4 monitors, that are capable of identifying patients with Cheyne-Stokes respiration, central sleep apnea, and complex sleep apnea;
- Evaluate the accuracy of the AHI and respiratory event information reported by CPAP and autoCPAP units.

7. Ensure Adequate Training and Education of Providers and Patients Regarding Ambulatory Management of OSA

Discussants highlighted concerns regarding the declining numbers of new clinician-scientists entering Sleep Medicine. There is increasing difficulty with recruitment of trainees through traditional pathways such as pulmonary medicine given prolonged training requirements for pulmonary, critical care, and sleep medicine. Innovative approaches to training and recruitment must be identified and pursued. Development of research networks would provide the required infrastructure to support high-quality training programs and promote recruitment to the field. Research training for new scientists will require energetic and dedicated mentors to guide and nurture the careers of fellows and junior faculty. Academic sleep centers need to obtain research training grants from governmental and institutional funding sources that will allow trainees to prepare for careers in sleep research.

The increased use of portable monitoring will elevate the role of generalists and other nonsleep medicine physicians. The level of education and training of such practitioners will critically influence optimum care of patients with OSA. Clinical practice networks where nonspecialized practitioners operate in close collaboration with a specialized sleep center offer one potential solution. More broadly, continuous education and training of practitioners outside of sleep centers is important; opportunities through multidisciplinary training programs and

clinician and research clerkships at other institutions should be established. Such programs should be directed not only to physicians, but to other members of multidisciplinary care teams including nursing, respiratory therapy, and sleep technologists.

Priority 7. Ensure adequate training and education of providers and patients regarding ambulatory management of sleep apnea. Recommendations:

- Stakeholder medical specialty organizations and the ACGME urgently need to negotiate innovative solutions to optimize the feasibility and appeal of sleep clinician-scientist training pathways;
- Increase investment in research training for new scientists;
- Develop and validate training programs for healthcare providers, including sleep specialists, primary care providers, physician extenders and allied health professionals.

8. Identify Funding Sources to Support the Needed Research

Closely related to the need to establish research networks to conduct adequately powered, multicenter clinical research studies (Priority 1) is the need to identify funding sources to support the research. Speakers from three different government organizations discussed research network infrastructure as well as funding opportunities for future research studies in portable monitoring: David Lanier, M.D., Center for Primary Care, Prevention and Clinical Partnerships, Agency for Healthcare Research and Quality (AHRQ), who spoke on PBRN's; G. Iris Obrams, M.D., M.P.H., Ph.D., National Center for Research Resources (NCRR), National Institutes of Health (NIH) who spoke on CTSAs; and Katherine Bent, R.N., Ph.D., C.N.S., Office of Research and Development, Department of Veterans Affairs (VA) who highlighted approaches to research funding within the VA system.

In the small group discussions on potential funding sources for portable monitor research, the key issues brought forward were to identify, cultivate, and amalgamate funding sources for portable monitoring research. There was also discussion concerning the translation of research findings into policy and practice. In this regard, it will be essential to eliminate monetary interest for sleep physicians who are making management decisions (i.e., eliminate conflict of interest). It will also be necessary to identify sources of funding for equipment, personnel, training, and infrastructure for application of innovative ambulatory management strategies. As noted in SECTION IV above, high-quality outcomes-based research demonstrating efficacy and cost effectiveness should serve as an important impetus for health management and insurance industries to provide support for these approaches.

In further discussion on research funding, the Center for Medicare and Medicaid Services was identified by participants as a source for research funding through Coverage with Evidence Development (CED). It is noteworthy that in the National Coverage Decision on coverage of CPAP therapy based on ambulatory monitor diagnosis released shortly after this Workshop was held (19), the Coverage with Evidence Development provision was made for adult beneficiaries who do not qualify for CPAP coverage based on standard criteria but who are enrolled in a study that addresses one of the following two questions:

> (a) In Medicare-aged subjects with clinically identified risk factors for OSA, how does the diagnostic accuracy of a clinical trial of CPAP compare with PSG and Type II, III, and IV home sleep test in identifying subjects with OSA who will respond to CPAP?
> (b) In Medicare-aged subjects with clinically identified risk factors for OSA who have not undergone confirmatory testing with PSG or Type II, III, and IV home sleep test, does CPAP cause clinically meaningful harm? (19)

Other aspects of ambulatory management of OSA may also prove to be appropriate for Coverage with Evidence Development funding, and the Center for Medicare and Medicaid Services should evaluate the indications for such funding on an ongoing basis.

Although some progress is being made in this area, public funding agencies and respiratory and sleep societies should increase funding to target the research priorities identified in this document. In particular, Workshop participants felt strongly that the NHLBI/National Centre for Sleep Disorders Research should prioritize an RFA on ambulatory management of OSA.

Priority 8. Identify funding sources to support the needed research. Recommendations:

- Identify, cultivate and amalgamate funding sources for portable monitoring research from NIH, AHRQ, CMS, private foundations, insurance industry, and manufacturers.
- Return the investment by conducting high-quality outcomes-based research to demonstrate the efficacy and cost effectiveness of portable monitor testing thereby generating the data needed by these funding sources for their decision making regarding healthcare policies and directions for future research and development.

VI. CONCLUSION

Pressure for alternative approaches to current recommended in-laboratory management of patients with OSA will continue to increase given the cost of PSG and the limited number of laboratory facilities relative to patient need. In addition, clinical demand for more rapid access to testing increases with the growing evidence that treatment of OSA improves functional and cardiovascular outcomes. What role will portable monitors assume and will this be based on a solid foundation of evidence or acceptance based on unavailable resources and familiarity of use? While attempting to validate portable monitors, we need to understand the significant clinical limitations of PSG and work to further standardize the sensors, signal processing, and CPAP titration protocols used in this so-called "gold-standard" test. Similar efforts are needed to further standardize portable monitors, especially to allow study results to be compared across monitors. More prospective, high-quality clinical trials are needed to compare home versus in-laboratory testing in terms of treatment outcomes in diverse patient populations. Cost-effectiveness protocols should be routinely incorporated into these clinical trials to collect the data that will allow for the development of decision-analysis models based on facts rather than assumptions. A rational first step would be to target portable monitors to include but not exclude the diagnosis of OSA. Current portable-monitor technology seems to be most applicable in

populations having a high likelihood of OSA. Alternative approaches should also be made available to underserved and remote populations that do not have access to gold-standard testing. Creation of practice-based networks might be one method for collecting the needed data in healthcare systems that offer traditional and alternative clinical pathways (69). Finally, one can predict that the rapid evolution and expansion of the discipline of Sleep Medicine into a multidisciplinary specialty is another potent force that will drive the practitioners to alternative testing methods. As physicians in Family Practice and Otolaryngology join Pulmonologists, Psychiatrists, and Neurologists to specialize in Sleep Medicine, the desire to test populations outside of the sleep center will increase. High-quality research will be needed to guide the systematic development of these alternative clinical disease-management pathways.

This statement was written by the Steering Committee of the ATS/AASM/ACCP/ERS Workshop on Research Priorities in Ambulatory Management of Adults with Obstructive Sleep Apnea.

Members of the Steering Committee

Samuel T. Kuna, M.D. (*Chair*) (ATS)
M. Safwan Badr, M.D. (ATS)
R. John Kimoff, M.D. (ATS)
Clete Kushida, M.D., Ph.D. (AASM)
Teofilo Lee-Chiong, M.D. (ACCP)
Patrick Levy, M.D., Ph.D. (ERS)
Walter T. McNicholas, M.D. (ERS)
Patrick J. Strollo, Jr. M.D. (AASM)

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The other members of the Workshop were:

Donna L. Arand, Ph.D.
John Atkinson, B.S., R.P.S.G.T.
Charles W. Atwood, M.D.
Ferran Barbe, M.D.
Kate Bent, R.N., Ph.D., C.N.S.
Elise Berliner, Ph.D.
Richard Berry, M.D.
Brian Boehlecke, M.D.
Alejandro Chediak, M.D.
Nancy Collop, M.D.
Michael Coppola, M.D.
Stephen Crane, Ph.D., M.P.H.
Mark D'Angelo
David D'cruz
Henry Glick, Ph.D.
Ronald Grunstein, M.D., Ph.D.
Indira Gurubhagavatula, M.D., M.P.H.
Conor Heneghan, Ph.D.
Thomas Hurwitz, M.D.
Meir Kryger, M.D.
David Lanier, M.D.
John Leteria
Michael Littner, M.D.
Geraldo Lorenzi-Filho, M.D.
Kimberly G. Love, L.T.J.G.
Douglas R. McEvoy, M.D.
Merrill Mitler, Ph.D.
Andrew A. Monjan, M.D., M.P.H.
Mary Morrell, M.D.
Naim Munir, M.D.
Terry Murphy
Tim Murphy
G. Iris Obrams, M.D., M.P.H., Ph.D.
Allan I. Pack, M.B., Ch.B., Ph.D.
Thomas Penzel, Ph.D.
S. Ramalingam, M.D., M.B.A.
Susan Redline, M.D.
John E. Remmers, M.D.
Carol L. Rosen, M.D.
Jeffrey Rubins, M.D.
Frank Ryan, M.D.
Preetam Schramm, Ph.D.
Frederic Series, M.D.
Thomas Smalling, Ph.D., R.R.T.
Ann Tisthammer, B.S., R.R.T.
Sean Tunis, M.D., M.Sc.
Michael Twery, Ph.D.
Christopher Valerian, D.O.
Edward Weaver, M.D.
Philip Westbrook, M.D.*
William Whitelaw, M.D.

* Dr. Westbrook was unable to attend the meeting

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