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The INCATM (Inhaler Compliance AssessmentTM): A comparison with established measures of adherence.

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Abstract

Objective

To compare the Inhaler Compliance Assessment™ (INCA™), a novel audio-recording device objectively measuring timing and proficiency of inhaler use, against established adherence measures, and explore its discriminant and predictive validity.

Design

Prospective observational study; 184 chronic obstructive pulmonary disease (COPD) patients used an INCA™-enabled salmeterol/fluticasone inhaler for one-month post-hospital discharge.

Main Outcome Measures

INCA™ (Attempted, Attempted Interval, Actual) adherence correlated with Doses Used Rate, self-reported adherence and prescription refill for concurrent validity. Discriminant validity for reason for admission, cognition and lung function; predictive validity for health status and quality-of-life.

Results

Rates of Attempted, Attempted Interval and Actual adherence were 59%, 47% and 23%, respectively. Only 7% of participants had Actual adherence >80%. INCA™ variables significantly correlated with Doses Used Rate but not with self-report; Attempted and Attempted Interval were weakly associated with prescription refill. Higher cognitive and lung functioning groups had better INCA™ adherence. Attempted and Attempted Interval predicted health status, while Doses Used Rate predicted quality-of-life.

Conclusion

INCA™ did not strongly correlate with self-report or prescription refill data. Discriminant and predictive validity demonstrated by INCA™ suggests the potential utility of the INCA™ as a method to identify intentional and unintentional adherence to inhaled medication and facilitate targeted intervention.

Key Words: chronic obstructive pulmonary disease (COPD); adherence; inhaler; electronic monitor; construct validity; predictive validity

Introduction

Chronic Obstructive Pulmonary Disease: Symptoms, Prevalence, and Impact

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory disease characterised by progressive airflow limitation and abnormal inflammatory response in the lungs (Rabe et al., 2007). Predominant symptoms of the disease include dyspnoea, cough and sputum production, which cause considerable impairment in daily functioning and exercise capacity (Mewes, Rief, Kenn, Ried, & Stenzel, 2016). Global prevalence of COPD is projected to increase; such that by 2020, COPD is predicted to be the third leading cause of death, and fifth leading cause of disability worldwide (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). The chronic, progressive and debilitating nature of COPD, alongside its high prevalence, confers significant burden on the healthcare system (Bourbeau & Bartlett, 2008). Infections and other exposures cause a worsening of symptoms, leading to exacerbations. For example, respiratory diseases, including COPD, are the third most common indication for acute hospital admission in Ireland (Irish Thoracic Society, 2013). Aside from the costs incurred, repeated exacerbations impact both the clinical course of the disease and patient quality of life.

Inhaler Adherence

Although COPD cannot be cured, optimal management with inhaled bronchodilator therapy (including salmeterol-fluticasone) provides symptom relief, reduces exacerbations and slows disease progression; thereby, improving health-related quality of life (Bryant et al., 2013; Nannini, Cates, Lasserson, & Poole, 2007). However, treatment efficacy does not represent real-world effectiveness, and one of the major variables that may explain this gap concerns medication adherence. Medication adherence is defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a medication regimen' (Cramer et al., 2008). Adherence to inhaled medication has two major components: 'temporal adherence' (the deliberate initiation of medication use at the correct time and intervals) and 'technique adherence' (correct implementation) (Bryant et al., 2013; Holmes, D'Arcy, Costello, & Reilly, 2014). Suboptimal adherence may therefore arise from non-use, over-use or under-use (which could also be conceptualised as intentional non-adherence), or due to poor inhaler technique, forgetting or misunderstanding of the treatment regimen, factors which are not under conscious control of the individual (or unintentional non-adherence). Intentional non-adherence may be driven by conscious decision-making processes in which individuals

choose to limit, modify or cease treatment (DiMatteo, Haskard-Zolnierek, & Martin, 2012; Phillips, Cohen, Burns, Abrams, & Renninger, 2016).

Estimates of adherence within COPD vary widely depending on the definitions and measures used, with reported rates of 70-90% in clinical drug trials and 20-60% in observational studies (Blackstock, ZuWallack, Nici, & Lareau, 2016; Di Martino et al., 2014). Moreover, inhaler technique is poor among COPD patients (Bonini & Usmani, 2015).

A recent systematic review demonstrated a significant association between non-adherence to COPD medication and adverse outcomes including mortality, increased hospitalisations, impaired quality of life and reduced productivity (van Boven et al., 2014). Furthermore, studies have shown a significant association between non-adherence to salmeterol/fluticasone, as measured by the inhaler dose-counter, and increased hospital readmissions and mortality (Vestbo et al., 2009).

Measuring Medication Adherence

In order to improve medication adherence, it is vital to first assess it accurately. A challenge in doing this, however, concerns the lack of consensus between researchers and clinicians on which tools are most appropriate to quantify the extent of adherence (Lam & Fresco, 2015). Currently, there exist several ways to assess adherence to inhaled medications.

The most common method is patient *self-report* whereby patients subjectively evaluate their own medication-taking behaviours. This can provide real-time feedback and identify individual concerns (Lam & Fresco, 2015). Although simple and inexpensive to administer, self-report has been shown to be susceptible to considerable reporting biases. Patients may under-report their level of non-adherence for a myriad of deliberate or accidental reasons (Lam & Fresco, 2015), including social desirability or recall biases.

Alternatively, objective *medication checks* such as pharmacy reconciliation, prescription refill rates and drug counter checks are also used to quantify adherence (Lam & Fresco, 2015). These methods are useful tools for helping to predict future health care utilisation and costs (Karve et al., 2009; Sattler, Lee, & Perri, 2013). However, they are undermined by the assumption that refilling a medication corresponds to actual medication-taking behaviour, and do not provide information about when or how medication is actually taken. Another simple objective method is the traditional *dose-counter* window on the side of an inhaler, which counts the number of doses taken by a participant. However, these methods do not capture important information on everyday inhaler use, from timing patterns to

technique of use, or other aspects such as medication dumping. Consequently, these measures tend to overestimate adherence (Sulaiman et al., 2016; WHO, 2003).

Electronic monitors address some of these limitations (Chan, Harrison, Black, Mitchell, & Foster, 2015). These monitors record the timing and frequency of inhaler drug administration, allowing for evaluation of drug taking patterns. For example, measurement from such devices is sometime disaggregated into indices of medication taking 'initiation', 'execution' and 'persistence'(Phillips et al., 2016). However, simply opening a medication does not ensure its subsequent use or that it was taken correctly. These monitors do not capture time of use in conjunction with technique of use, which is essential for true drug delivery (Sulaiman et al., 2016).

The limitations of the aforementioned adherence measures preclude their widespread utility as a gold standard for quantifying adherence. There is a need for a more sophisticated technology that can objectively measure both when and how an inhaler has been used, and discriminate between intentional and unintentional adherence. On the basis of this need, a novel device named the Inhaler Compliance Assessment™ (INCA™) was developed.

The Inhaler Compliance Assessment™

The INCA™ is a mobile technology audio recording device, fitted to a Diskus™ inhaler, comprising a small battery powered microphone, solid-state memory storage and a microprocessor (D'Arcy et al., 2014), see Figure 1. Opening the inhaler initiates an electronic acoustic file that records the audio associated with the inhalation. This recording terminates once the inhaler is closed. The audio files are time-stamped and stored on a memory platform until the device is uploaded to a PC. Subsequent processing and analysis of the audio files is conducted by an automated algorithm incorporating signal processing, with time-series analysis. This provides quantitative output information on technique, time, and duration of inhaler use (see Figure 2 for sample output). The audio recordings for the first 60 patients were over-read by two independent expert raters (observer agreement >80%), and the remaining patients' audio files were over-read by a single expert-rater. This over-read data was subsequently used to calculate adherence. Detail on the sensitivity of the calculations and level of agreement between the two raters, and between the raters and the algorithm, have been previously published (Holmes et al., 2014; Holmes et al., 2013; Seheult, Costello, et al., 2014; Seheult, O'Connell, et al., 2014).

The acoustic data allows identification of each step of inhaler use and can therefore detect technique errors such as failure to prime the inhaler, dispersion of the medication by exhaling into the mouthpiece, low inhalation flow, dose dumping, and so on. In previous work, the accuracy of the INCA^{TM} algorithm for detecting technique errors has been validated in community dwelling asthmatic patients (Holmes et al., 2013) and against two expert human raters (Holmes et al., 2014), and with peak inspiratory flow, which correlates with the amount of drug delivered (D'Arcy et al., 2014; Seheult, Costello, et al., 2014; Seheult, O'Connell, et al., 2014). Therefore, output from the INCA^{TM} offers a precise and objective method of monitoring true drug delivery over time in an uncontrolled real-world environment, and can therefore distinguish intentional temporal non-adherence (e.g. Figure 2(d)) from unintentional technique non-adherence (e.g. Figure 2(b)). However, no study yet has compared the INCA^{TM} with established measures of adherence, such as the inhaler dose-counter, self-report or prescription refill.

The Present Study

The present study aims to evaluate the association among traditional medication adherence measures and INCA^{TM} estimates of adherence to bronchodilator therapy, specifically a salmeterol/fluticasone Diskus^{TM}, in COPD. In particular, this project will firstly evaluate the concordance between adherence as measured by the INCA^{TM}, dose-counter, self-report and prescription refill records to establish concurrent validity. Then, we explore the discriminant validity of the adherence measures for distinguishing known groups of clinical importance, and examine predictive validity of adherence measures for functional health outcomes (health status and disease-specific quality of life).

Methodology

Study Design and Procedure

A prospective observational study design was used. The data analysed were collected as part of a broader, on-going research study investigating adherence to a regularly prescribed combination long acting beta-agonist/inhaled corticosteroid inhaler (salmeterol/fluticasone) by patients with COPD, following hospital discharge (Sulaiman et al., 2016). Between February 2012 and February 2016, data were collected in a large single-centre academic teaching hospital in [name withheld for peer-review].

Consecutive patients with an established diagnosis of COPD, already prescribed a salmeterol/fluticasone Diskus™ inhaler and admitted to hospital for any reason, were identified on the wards and screened by the investigator to determine eligibility. Exclusion criteria included residence in a nursing home and/or severe cognitive impairment (scores of less than 10 on the Montreal Cognitive Assessment (MoCA) (The Montreal Cognitive Assessment, 2009). At recruitment, consenting participants were provided with a new 60-dose salmeterol/fluticasone Diskus™ inhaler fitted with an INCA™ device, and completed a number of assessments with the investigator (duration approximately 20 minutes). Prior to discharge, participants were shown the correct use of their inhaler, and were asked to use it as demonstrated, twice per day at regular 12-hourly intervals, for the subsequent month. Participants were contacted by telephone at one-month (between 26 and 30 days following recruitment) to arrange collection of the inhaler via a courier. During this phone interview, participants also completed a number of follow-up assessments.

Prescription refill adherence data for salmeterol/fluticasone and aspirin were collected retrospectively from the Health Services Executive Primary Care Reimbursement Scheme (HSE-PCRS). The HSE-PCRS is a pharmacy claims database detailing monthly dispensed medications for individuals on the General Medical Services (GMS) scheme (a means-tested scheme providing free health services and medication cover for eligible individuals in [name withheld for peer-review]). The study flow is illustrated in Figure 3. The [name withheld for peer-review] approved this study.

Measures

Socio-demographic Factors

Socio-demographic information (including age, sex, body mass index (BMI) and smoking history) was collected during hospital admission. Data on level of social support was also recorded including access to public or private health insurance, living alone, having a carer and frailty factors (has a stair lift, has a bedroom downstairs, gets meals delivered or has a carer) (Sulaiman et al., 2016).

Disease Severity Factors

Data on pulmonary function [forced expiratory volume in one second (FEV1), as litres (L) and percentage predicted (%)], were extracted from the patients' medical charts during hospital admission. Cough peak expiratory flow rate (PEFR; L/min) was measured at

recruitment. Participants exhaled into a handheld device (Mini-Wright Clement Clarke International Ltd) with maximum force, from a sitting position and following a deep inhalation. Better lung function was indicated by a high PEFR. Peak inspiratory flow rate (PIFR), measuring the strength and speed exerted by an inhalation, was also measured at recruitment.

Clinical and Treatment Characteristics

Comorbid and mortality risk status was recorded using the Charlson Comorbidity Index, a measure of disease burden calculated by classifying co-morbid conditions and weighting them from one to six according to their adjusted risk of mortality. Scores range from 1-16, with scores greater than 8 indicating a high level of comorbidity (Charlson, Pompei, Ales, & MacKenzie, 1987). The RxRisk model, a pharmacy-based risk-assessment tool was retrospectively calculated from the HSE-PCRS database using an algorithm that groups prescription refills into chronic disease classes (Fishman et al., 2003).

Information on cognitive function was also collected at baseline using the MoCA (Nasreddine et al., 2005), a 30-point assessment testing several cognitive domains including visuospatial/executive function, naming, attention, language, abstraction, delayed recall and orientation. The MoCA is a widely used screen for cognitive impairment with a recommended cut-off of <24 in the Irish population, (O'Caoimh, Timmons, & Molloy, 2016).

At recruitment, data regarding treatment (including salmeterol/fluticasone dose, cause of admission, length of stay, number of nebulisers and medications prescribed) were retrieved from the patients' medical charts. Prior to discharge, inhaler technique was also assessed through direct observation by the investigator using a 10-step checklist named the Inhaler Proficiency Scale (Mac Hale & Cowman, 2012). The IPS includes five items on correct handing and positioning of the inhaler, four items on correct inhalation and exhalation technique, and one item on gargling after use; these items were graded Yes/No based on correct execution.

Adherence Measures

INCA™ Adherence. Analysis of the INCA™ audio files by automated signal processing techniques provided information on timing of use and the interval between doses**.** Following this, data on time, interval between doses and technique were amalgamated to generate an area under the curve (AUC) metric, by a trapezoidal function; this method of

adherence calculation has been previously described (Sulaiman et al., 2016). In brief, the AUC was calculated for participants' *Attempted* adherence; that is, the number of times participants primed their inhaler and attempted to use it; *Attempted Interval* adherence; that is, evidence of drug priming at the correct intervals; and *Actual* adherence, which accounts for critical technique errors and is a measure of true medication delivery (incorporating intentional and unintentional nonadherence) (Sulaiman et al., 2016).

Dose-Counter Adherence. The *Doses Used Rate* was calculated by reading the number of doses taken (out of a possible 60 doses) multiplied by 100.

Self-reported Adherence. The Morisky Medication Adherence Scale (MMAS) (Morisky, Ang, Krousel-Wood, & Ward, 2008) is a widely-used 8-item scale used in the present study to measure self-reported adherence. The first 7 questions were answered with a dichotomous Yes/No response, while the final item was answered using a five-point Likert scale (ranging from 'Rare/ never' to 'All of the time'). The MMAS total ranged from zero to 8, where 8 indicated high self-reported adherence. The MMAS was further classified into high (score of 8), medium (score of 6 to <8) and low adherence (<6) as recommended (Morisky et al., 2008). The MMAS has demonstrated good reliability (Cronbach's alpha= 0.83), and using a cut-off of six, good sensitivity and specificity for identifying good and poor adherers (Morisky et al., 2008). In the present study, the MMAS was administered at one-month follow-up.

Prescription Refill Adherence. Prescription refill adherence to salmeterol/fluticasone was retrospectively attained for a 12-month period prior to study enrolment for all participants holding a GMS card. Data on prescription refill adherence to oral aspirin was also obtained as a comparator drug, as most patients would be prescribed this as part of the COPD treatment regimen. Adherence rates were assessed using medication possession ratio (MPR) and proportion of days covered (PDC) calculations. MPR is a ratio of the proportion of doses obtained relative to the dispensing period (sum of days a medication is supplied over a set period, divided by the number of days in the period, multiplied by 100) (Karve et al., 2009; Lam & Fresco, 2015). PDC is the accumulation of days the medication is available (or 'covered') within a pre-determined observation period, divided by the number of days in that period, and multiplied by 100. MPR and PDC were used as continuous variables and also as dichotomised variables using ≥80% as a widely used cut-off between good and poor adherers (Karve et al., 2009; Sattler et al., 2013).

Outcome Measures

Health Status. The COPD Assessment Test (CAT) (Jones et al., 2009) was administered at baseline and one-month follow-up and is a patient-completed questionnaire measuring the global impact of COPD on health status. The questionnaire comprises 8 items assessing domains of disease severity (cough, sputum production, dyspnoea, and chest tightness) and impact on daily functioning (capacity for housework, confidence leaving the house, quality of sleep, and energy levels). Patients rated these items on a six-point scale (from one to five, e.g. zero 'I never cough' to five 'I cough all the time'). Total scores ranged from zero to 40, where higher scores were indicative of greater disease burden. The CAT has demonstrated excellent psychometric properties, including very good internal consistency (Cronbach's alpha= 0.88) and test-retest reliability (intra-class correlation coefficient= 0.8) (Jones et al., 2009).

Disease-Specific Quality of Life. The Medical Research Council (MRC) Dyspnoea scale (Fletcher, 1959) was also performed at baseline and follow-up and is a quick and easy to administer questionnaire grading the patients' perceived disability associated with breathlessness. It comprises five statements and yields an ordinal score ranging from one 'I only get breathless with strenuous exercise' to five 'I am too breathless to leave the house'. The MRC is widely used and has been shown to predict survival (Nishimura, Izumi, Tsukino, & Oga, 2002).

Statistical Analysis

Only participants with data available on both INCA™ and prescription refill adherence measures were included in this analysis (n=184). Descriptive statistics were utilised to describe the demographic and clinical characteristics and adherence estimates. Continuous variables were summarised using means and standard deviations (S.D.), and medians and interquartile ranges (IQR) for non-normal or ordinal data. Frequencies and percentages are presented for categorical variables. For variables where the data were not normally distributed, a log transformation was conducted in order to achieve normality. Subsequent analyses were performed with this data on a log scale. For scores of zero, when a log transformation was not possible, a value of 0.01 was imputed. Concurrent validity was assessed using Pearson Product-Moment correlations for continuous variables, point biserial correlations for continuous and binary variables, and phi correlations for two binary variables. A 'known-groups' approach (Hays, 1998) was employed to examine discriminant

validity. A priori, groups were dichotomised cause of admission (COPD exacerbation, other reason); cognitive function (MoCA ≥ 24 normal, <24 cognitive impairment) and lung function (Cough PEFR ≥150 good, <150 poor). Post-hoc, we also assessed by smoking status (Yes/No), living alone (Yes/No), and having a carer (Yes/No). Independent samples t-tests assessed between-group differences on adherence variables. Finally, regression analyses predicted health outcomes at one-month follow-up. Continuous independent variables were standardised for ease of interpretation. Linear and ordinal regressions, adjusting for baseline CAT and baseline MRC, using robust variance estimators, predicted scores on the CAT and MRC respectively at follow-up. Data were analysed using Stata Version 10.0 (StataCorp, 2007).

Results

Baseline Characteristics

A total of 184 participants with data available on both INCA™ and prescription refill adherence measures were included in this analysis (see Figure 3 for a consort diagram detailing study participation). Socio-demographic and clinical characteristics are provided in Table 1. In brief, participants were elderly with approximately half female. Eighty percent of participants had a GMS card. The sample had a mean pack years smoked of over 60 years, with a fifth still smoking. Participants had substantial COPD-related disability and impairment at baseline. In addition to their COPD, participants showed considerable burden of co-morbid conditions, and were prescribed a high number of regular medications.

Adherence

Adherence summary statistics are shown in Table 1. Using the AUC method for calculating INCA™ adherence, the rate of Attempted adherence observed over the study period was 59%. When interval between doses was included, Attempted Interval adherence was 47%. Despite relatively good observer-rated inhaler technique at discharge (as per IPS checklist), once technique was incorporated into the adherence calculation alongside timing of use, the mean rate of Actual adherence was only 23%. Only 7% of participants had Actual adherence greater than 80%. Of the 60 doses expected over the follow-up period, the mean number of doses attempted, as measured by the dose-counter, was 46 doses. This corresponds to 77% of doses used.

Approximately a third of participants self-reported reported a ‘high’ level of adherence, a further 46% reported ‘medium’ adherence and only a fifth reported ‘low’ adherence as per the MMAS.

The mean MPRs for salmeterol/fluticasone and aspirin were 76% and 81%, respectively. Comparable PDC rates were observed, with 74% for salmeterol/fluticasone and 81% for aspirin. Using 80% as a cut-off for good adherence, approximately 60% of participants demonstrated good MPR and 58% had good PDC adherence to their inhalers. No statistically significant differences between salmeterol/fluticasone and aspirin MPR rates (t (119) = -0.91, p= 0.364) or PDC rates (t (119) = -1.21, p= 0.230) were observed.

Outcome Measures

The means (S.D.) for health status (CAT) at baseline and one-month follow-up were 20.96 (7.83) and 20.00 (8.07), respectively. The median (IQR) statistics for disease-specific quality of life, as measured by the MRC, were 4 (1) at baseline and similarly, 4 (1) at follow-up.

Concurrent Validity

Doses Used Rate, as measured from the inhaler dose-counter, was significantly strongly correlated with Attempted, Attempted Interval and INCA^{TM} adherence (Table 2). No significant correlations were observed between self-report and INCA^{TM} adherence variables. Attempted adherence was weakly correlated with MPR and PDC for salmeterol/fluticasone. Similarly, Attempted Interval adherence was weakly associated with salmeterol/fluticasone MPR and PDC. Actual adherence, however, was not significantly related to salmeterol/fluticasone MPR or PDC.

Discriminant Validity

A known-groups comparison approach was used to establish discriminant validity (see Table 3). Participants with normal or impaired cognitive function were observed to be significantly different on Attempted, Attempted Interval, Actual and Doses Used Rate adherence, with higher adherence for participants with normal cognitive function. No significant differences were observed between these participants on the self-report or prescription refill variables.

In comparing lung function groups, participants with high and low Cough PEFR differed significantly on Attempted, Attempted Interval, and Actual adherence; that is,

participants with higher Cough PEFR had correspondingly better INCA™ adherence. No such differences were established between these participants on dose-counter, self-report or prescription refill adherence variables.

Participants who reported living alone differed significantly on Attempted and Attempted Interval adherence, with poorer adherence observed for those living alone, as compared with their supported counterparts. No significant differences were observed between these participants on the self-report or prescription refill variables.

No significant differences were observed between participants who: 1) were admitted for a COPD exacerbation or for another reason; 2) were still smoking at time of enrolment with those who had quit; or 3) had a carer, on any of the adherence measures.

Predictive Validity

Only INCA™ Attempted and Attempted Interval adherence were predictors of health status (CAT) at follow-up, although these associations were weak (Table 4). In addition, the only significant predictor of disease-specific quality of life (MRC) was the Doses Used Rate (Table 5).

Discussion

This was a prospective observational study examining the concurrent, discriminant and predictive validity of the INCA™ device, a novel objective adherence measure. INCA™ Actual adherence was low, with only 7% of participants using their inhaler regularly and correctly greater than 80% of the time. In examining concurrent validity, we compared the INCA™ to established measures of adherence, namely self-report and prescription refill. We found no association between INCA™ and self-reported adherence, and small associations with adherence measured by prescription refill. Examination of discriminant and predictive validity showed the INCA™ to have good clinical utility, in that the INCA™ was the only adherence measure to discriminate between good and poor adherence on important disease severity indicators, and to predict patient health status.

Importantly, the INCA™ was uniquely able to distinguish between intentional and unintentional adherence (arising from poor technique error). The discordance between INCA™ Attempted and Actual adherence highlights the importance of examining technique (unintentional non-adherence) in conjunction with timing of use (intentional non-adherence).

Analysis of the audio recordings from the INCA™ device revealed that, in the month immediately following hospital discharge, both temporal and technique non-adherence to preventer inhaled therapy was common. Less than 60% of patients attempted to use their inhaler, indicating a high rate of intentional non-adherence in this sample. Less than 50% attempted to use the inhaler at the correct time intervals, and once inhaler technique was incorporated, this figure dropped substantially to 23% actual adherence. Moreover, from a clinical perspective, only 7% of participants used their inhaler as prescribed more than 80% of the time, indicating a concerning rate of unintentional non-adherence. Despite repeated instruction on inhaler technique during admission, as per hospital policy, and despite good technique as measured by direct visual assessment (IPS checklist), poor technique was prevalent among this population once in an uncontrolled real-world environment. The considerably low level of actual adherence identified contrasts sharply with the high rates of adherence observed by other measures. For instance, the MPR and PDC rates of prescription refill adherence were high (76% and 81%, respectively). Moreover, the majority of participants subjectively reported a medium to high level of adherence, an unsurprising finding as self-report has been shown to consistently yield higher rates of adherence compared to objective measures (Berg & Arnsten, 2006). This discordance between adherence estimates by different measures highlights the limited real-world applicability of the previously established measures of adherence tested in this study, and highlights that the INCA™ is a superior measure of adherence than the others tested in this study.

Using a known-groups approach, discriminant validity of the INCA™ for clinically important features was established; good adherers had better cognitive and lung function than their poor adherer counterparts, and were more likely to live with others, which perhaps reflected increased social support. However, no significant differences were observed when comparing high or low MPR, PDC or self-report groups on these clinical and social characteristics. Interestingly, no significant differences on adherence were observed by smoking status. It may be that, in addition to the complexity of inhaler adherence, smoking cessation may be a complex behaviour to incorporate into a treatment regimen due to its addictive nature, and thus may be a recommendation only adhered to by a small proportion of the sample. Only the INCA™ attempted variables were predictive of health status, and the Doses Used Rate predictive of disease-specific quality of life at follow-up, albeit weakly. It is surprising that no association was observed for actual adherence and disease-specific quality of life, given the observed association between quality of life and Doses Used Rate.

However, it may be that those with better health status represented those who were more clinically well and may have been better able to follow the instructions for correct inhaler use, and thus had higher quality of life at baseline assessment. It is important to note here that only 7% of the sample demonstrated actual adherence in terms of adequate delivery of the drug to the lungs, hence the observed associations are derived from a small sample.

This study had a number of strengths. We examined a large COPD cohort in an uncontrolled real-world environment, and applied several measures of adherence, allowing for a comprehensive investigation of validity using one subjective and two objective measures. Additionally, this study measured adherence with a specifically developed objective adherence measure for inhalers. The INCA^{TM} is a novel adherence measure; capable of objectively monitoring patterns of intentional temporal and unintentional technique adherence in real-time. The incorporation of technique into the calculation of the Actual adherence allowed for a more comprehensive and accurate assessment of true medication delivery to be performed. In this way, the INCA^{TM} is a more sophisticated measure of adherence, improving upon some of the limitations of existing measures, i.e. the measurement of either timing or technique in isolation, reliance on patient self-report or examination of prescription refills.

We acknowledge some methodological issues. Firstly, the present study was conducted in a single-centre, with the majority of patients on the GMS scheme; this may have favoured a lower socio-economic group. Varying socioeconomic status and education history have been shown to influence rates of adherence (Golay, 2011); possibly limiting generalisability. However, the high proportion of patients with government-sponsored health insurance may also be indicative of the cohort's older age, disease-severity and high number of co-morbidities – clinical characteristics commonly observed in a COPD population. In addition, the INCA^{TM} examined medication adherence to only one pharmacological drug (salmeterol/fluticasone) using one method of administration (Diskus^{TM}). However, this specific focus enabled a comprehensive investigation of adherence to a commonly prescribed COPD treatment. It could be argued that participants may have changed their inhaler use as a consequence of study enrolment, however previous examinations of a potential Hawthorne Effect (Williams, Amico, Bova, & Womack, 2013) in adherence studies have shown this not to be the case (Sutton et al., 2014).

Whilst the INCA™, dose-counter and prescription refill measures provided data specifically on adherence to salmeterol/fluticasone, the items on the MMAS self-report scale weren't specific to inhaler use and examined medication adherence more generally. These variations may have contributed to the paucity of, or weak, associations observed between INCA™ and the self-report and prescription refill measures of adherence. However, aspirin was used as a comparator drug, as most participants were prescribed aspirin as part of their COPD medication regime and whilst the self-report measure used in this study did not specifically measure self-reported adherence to inhalers, there was no observed correlation between self-reported adherence and oral aspirin use, highlighting an overall lack of association between self-reported adherence and actual adherence. We acknowledge that the INCA™ may not fully explore the extent to which non-adherence may be a consequence of forgetting to take medication, particularly when considering the level of cognitive impairment observed in this cohort. Notwithstanding, the INCA™ is a potentially useful tool in the clinical setting for identifying and distinguishing volitional non-adherence from forgotten doses. The validity of self-reported adherence measures within cognitively impaired groups hasn't been established (van Dulmen et al., 2007), therefore future research avenues should explore the utility of established measures of adherence amongst those with cognitive impairment. Although the sample demonstrated a number of comorbidities, only 6% of the sample had high-risk comorbidity scores on the Charlson Co-morbidity Index, therefore the sample was underpowered to investigate the impact of high vs. low comorbidity on adherence. This potential relationship should be considered in future research. Furthermore, future research should seek to explore patient- and healthcare professional- perspectives on the use of the INCA™, which may tease out patients' perceptions of adherence to the treatment regimen and identify discrepancies with self-reported adherence. Finally, the duration of follow-up (one-month) may not have been sufficient to elicit substantial changes in health status and quality of life for the predictive validity analyses. Beliefs about value of the medication are meaningful predictors of non-adherence (DiMatteo et al., 2012) , and actual and perceived health status in the acute time period following a hospital admission may determine individual commitment to a complex treatment regimen, such as that in COPD (Phillips et al., 2016). Longer-term studies are required to more fully investigate the correlation between patient beliefs, INCA™ adherence and clinical parameters.

The unique ability of the INCA™ to objectively record temporal and technique adherence, alongside its significant association with peak inspiratory flow (D'Arcy et al.,

2014; Seheult, Costello, et al., 2014; Seheult, O'Connell, et al., 2014), demonstrates the potential utility of the INCA™ as a reliable method for monitoring true medication delivery within a real-world context. Moreover, the accuracy of the INCA™ for identifying intentional non-adherers, and technique errors, such as multiple inhalations, dose dumping, dispersion of the medication, and so on (Holmes et al., 2014; Holmes et al., 2013), will help clinicians decide if a Diskus™ is an appropriate mode of drug delivery for a patient. Additionally, the discriminant and predictive validity of the INCA™ is useful for identifying poor adherers and those at risk of adverse clinical outcomes. Individually tailored interventions are demonstrated to be superior to generic interventions in improving medication adherence (DiMatteo et al., 2012; van Dulmen et al., 2007). Personalised patient data from the INCA™ serves as a platform from which to initiate tailored personalised conversations around behaviour change. Discussion of feedback can elicit technique errors, personal barriers to adherence or beliefs regarding the efficacy of the prescribed treatment regimen. This form of personalised feedback in turn allows for intervention using appropriate behaviour change techniques (Michie et al., 2013) to address individual barriers, such as goal setting to improve timing of treatment (Interval Adherence), increasing motivation and/or clarifying beliefs in the efficacy of treatment (Actual Adherence).

Conclusion

Inaccurate assessment of adherence has direct implications for the interpretation of the effectiveness of a treatment. The present study provides evidence for the use of INCA™ as a novel adherence assessor; capable of objectively monitoring patterns of intentional temporal and unintentional technique adherence in real-time. Based on our findings, we suggest that the INCA™ is a more sophisticated measure of adherence, which improves upon some of the limitations of existing adherence measures, and has a potential useful role within clinical settings in the management of respiratory conditions.

Word Count: 5394

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The authors' responsibilities were as follows: LM, FD, GM, and RWC designed the research; RBR and RWC developed the electronic engineering and signal processing methodology; IS & RWC developed the INCA™ adherence calculation methods; LM, FD, IS, GG and RWC advised on the statistical analysis; CM was primarily involved in patient recruitment, data collection and data analysis; KB retrieved the prescription refill data and calculated MPR and PDC variables; CM and LM wrote the manuscript; LM had primary responsibility for the final content. All co-authors edited and approved this manuscript.

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Conflict of Interest Statement

Two of the authors (RBR and RWC) are named on a patent for the INCA™ device.

Disclosure Statement

The funder of this study played no role in study design, data collection, data analysis or the writing of this manuscript. RBR and RWC are named on a patent for the INCA™ device.

Tables

Table 1. Baseline socio-demographic, disease severity, clinical, treatment and adherence characteristics.

Variable	Total Sample (*N*= 184)
Socio-demographic Variables	
Age, years: mean (S.D.)	70.9 (9.65)
Male, n (%)	95 (51.6%)
BMI, mean (S.D.)	27.5 (6.17)
Current smoker, n (%)	34 (20.4%)
Ever smoker, n (%)	168 (99.4%)
Pack years smoked, mean (S.D.)	60.8 (47.2)
Living alone, n (%)	43 (26.7%)
Has a carer, n (%)	41 (24.6%)
Frailty score, median (IQR)	2 (2)
Disease Severity Variables	
FEV_1 (L), mean (S.D.)	1.33 (0.62)
FEV_1 (%), mean (S.D.)	53.1 (21.7)
Cough PEFR (L/min), mean (S.D.)	160.9 (100.0)
Peak Inspiratory Flow, mean (S.D.)	71.7 (27.8)
Clinical Characteristics	
Charlson Co-morbidity, mean (S.D.)	5.92 (1.84)
RxRisk Adult, mean (S.D.)	5.35 (1.86)
MoCA, mean (S.D.)	21.5 (5.08)
Treatment Factors	
Dose Salmeterol/Fluticasone, n (%)	
250mcg	40 (23.1%)
500mcg	133 (76.9%)
Cause of admission, n (%)	
COPD exacerbation	114 (62.3%)
Other	69 (37.7%)
Length of stay, days: mean (S.D.)	7.72 (9.08%)
Number of prescribed medications, median (IQR)	15 (9)
Number of nebulisers used, median (IQR)	1 (2)
Smoking cessation treatment, n (%)	38 (20.7%)
Inhaler Proficiency Score, mean (S.D.)	7.64 (1.58)
INCA™ Adherence	
INCA™ Attempted, %: mean (S.D.)	58.7 (29.7)

INCA™ Attempted Interval, %: mean (S.D.)	47.3 (33.4)
INCA™ Actual, %: mean (S.D.)	23.2 (29.0)
Doses Used Rate, %: mean (S.D.)	76.9 (28.9)
Self-reported Adherence (*n*= 83)	
MMAS Total 1 Month FU, mean (S.D.)	6.75 (1.41)
MMAS Categories 1 Month FU, n (%)	
High Adherence	29 (34.9%)
Medium Adherence	38 (45.8%)
Low Adherence	16 (19.3%)
Prescription Refill Adherence	
MPR Salmeterol-Fluticasone, %: mean (S.D.)	75.6 (31.4)
PDC Salmeterol-Fluticasone, %: mean (S.D.)	73.8 (32.6)
MPR Aspirin (*n*= 122), %: mean (S.D.)	81.1 (29.6)
PDC Aspirin (*n*= 122), %: mean (S.D.)	80.5 (30.0)
≥ 80% MPR Salmeterol-Fluticasone, n (%)	107 (59.8%)
≥ 80% PDC Salmeterol-Fluticasone, n (%)	104 (58.1%)
≥ 80% MPR Aspirin, n (%)	89 (73.0%)
≥ 80% PDC Aspirin, n (%)	87 (71.3%)
Baseline Outcome Measures	
CAT, mean (S.D.)	20.9 (7.83)
MRC, median (IQR)	4 (1)

Note. n, number of observations; S.D., standard deviation; BMI, body mass index; IQR, interquartile range; FEV_1, forced expiratory volume in one second; L, litre; PEFR, peak expiratory flow rate;CAT, COPD Assessment Test; MRC; Medical Research Council; MoCA, Montreal Cognitive Assessment; mcg, micrograms; COPD, Chronic Obstructive Pulmonary Disease; MMAS, Morisky Medication Adherence Scale; FU, follow up; INCA, Inhaler Compliance Assessment; MPR, Medication Possession Ratio; PDC, Proportion of Days Covered.

Table 2. Correlations between the adherence variables.

	1	2	3	4	5	6	7	8	9	10	11	12
1. INCA™ Attempted	-											
2. INCA™ Attempted Interval	.85***	-										
3. INCA™ Actual, Log10	.59***	.57***	-									
4. Doses Used Rate	.55***	.57***	.38***	-								
5. MMAS Total 1 Month FU	.07	.09	-.09	-.02	-							
6. MPR Salmeterol-fluticasone	.15*	.17*	.05	0.10	-.11	-						
7. PDC Salmeterol-fluticasone	.15*	.16*	.05	.10	-.11	.99***	-					
8. MPR Aspirin	-.04	-.03	-.13	-.02	-.21	.27**	.26**	-				
9. PDC Aspirin	-.05	-.04	-.14	-.02	-.19	.26**	.26**	.99***	-			
10. ≥ 80% MPR Salmeterol-Fluticasone	.20[a]**	.21[a]**	-.01[a]	.09[a]	-.11[a]	.86[a]***	.87[a]***	.21[a]*	.21[a]*	-		
11. ≥ 80% PDC Salmeterol-Fluticasone	.22[a]**	.21[a]**	.00[a]	.09[a]	-.08[a]	.85[a]***	.86[a]***	.26[a]**	.25[a]**	.97[b]***	-	
12. ≥ 80% MPR Aspirin	.01[a]	.02[a]	-.07[a]	-.01[a]	-.19[a]	.19[a]*	.19[a]*	.86[a]***	.85[a]***	.18[b]	.23[b]*	-
13. ≥ 80% PDC Aspirin	.03[a]	.03[a]	-.07[a]	-.02[a]	-.19[a]	.19[a]*	.19[a]*	.83[a]***	.84[a]***	.19[b]*	.24[b]**	.96[b]***

Note. INCA, Inhaler Compliance Assessment; MMAS, Morisky Medication Adherence Scale; FU, follow up; MPR, Medication Possession Ratio; PDC, Proportion of Days Covered.

[a] Point biserial correlation coefficient; [b] Phi correlation coefficient

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level; *** Correlation is significant at the 0.001 level

Table 3. Independent t-tests exploring the discriminant validity of the adherence measures using known-groups: a) Cause of admission; b) Cognitive function; c) Lung function; d) Smoking status; e) Living alone; f) Having a carer. Summary statistics are provided as Mean (Standard Deviation).

	MMAS Total 1 Month FU	INCA™ Attempted	INCA™ Attempted Interval	INCA™ Actual, Log10	Doses Used Rate	MPR Salmeterol/ Fluticasone	PDC Salmeterol/ Fluticasone
Cause of Admission							
COPD Exacerbation (*n*= 115)	6.96 (1.11)	61.1 (29.6)	49.9 (33.3)	0.91 (0.75)	77.5 (27.0)	73.9 (32.8)	71.7 (34.3)
Other Reason (*n*= 60)	6.50 (1.68)	53.2 (30.0)	41.5 (32.1)	0.84 (0.76)	74.7 (32.9)	79.4 (27.8)	78.3 (28.4)
p value	.155	.097	.106	.553	.554	.288	.215
Cognitive Function							
Normal (*n*= 70)	6.36 (1.62)	67.9 (25.5)	57.5 (29.8)	1.11 (0.71)	83.8 (25.6)	73.4 (32.6)	71.3 (33.9)
Impairment (*n*= 105)	7.00 (1.32)	53.9 (31.2)	40.9 (34.4)	0.73 (0.74)	72.3 (30.0)	77.8 (29.7)	75.9 (31.1)
p value	.071	.002**	.001**	.001***	.010**	.362	.363
Lung Function							
High Cough PEFR (*n*= 75)	6.55 (1.09)	64.8 (27.5)	53.9 (31.4)	1.12 (0.73)	80.7 (28.1)	76.2 (29.5)	74.7 (30.3)
Low Cough PEFR (*n*= 78)	6.84 (1.61)	50.7 (30.1)	36.1 (32.1)	0.62 (0.68)	74.8 (29.3)	73.5 (32.9)	71.3 (34.7)
p value	.411	.003**	<.001***	<.001***	.204	.613	.526
Current Smoker							
Yes	6.45 (0.35)	51.5 (28.9)	39.7 (30.9)	0.78 (0.64)	80.9 (26.2)	68.8 (33.7)	66.4 (34.9)
No	6.86 (0.17)	60.8 (28.9)	49.3 (33.2)	0.92 (0.77)	77.0 (28.7)	77.1 (30.1)	75.6 (30.9)
p value	.254	.098	.129	.317	.475	.168	.141
Alone at Home							

Yes	6.67 (1.58)	49.1 (30.3)	37.8 (32.2)	0.71 (0.72)	77.4 (30.7)	83.7 (25.6)	82.1 (26.2)
No	6.76 (1.35)	60.8 (27.7)	48.7 (32.6)	0.94 (0.75)	78.8 (27.3)	72.8 (31.8)	71.4 (32.7)
p value	.799	.022*	.0061**	.081	.791	.054	.065
Has a Carer							
Yes	6.47 (2.09)	58.6 (29.8)	46.3 (33.5)	0.73 (0.69)	72.3 (30.5)	79 (27.9)	78.7 (27.7)
No	6.84 (1.07)	59 (29)	47.7 (33.3)	0.94 (0.75)	79.7 (27.3)	74.5 (32.1)	72.4 (33.3)
p value	..293	.925	.819	.125	.148	.431	.279

Note. MMAS, Morisky Medication Adherence Scale; FU, follow-up; INCA, Inhaler Compliance Assessment; MPR, Medication Possession Ratio; PDC, Possession of Days Covered; COPD, Chronic Obstructive Pulmonary Disease; n, number of observations; PEFR, peak expiratory flow rate.
*Significant at the 0.05 level; **significant at the 0.01 level; ***Significant at the 0.001 level

Table 4. Linear regression models predicting scores on the CAT at one-month follow-up. Models are adjusted for baseline CAT score.

Model Number	Variable	R^2	β	95% CI	*p* value
	INCA™ Adherence				
1	INCA™ Attempted	.21	-1.35	-2.62 to -.08	.038*
2	INCA™ Attempted Interval	.21	-1.32	-2.56 to -.07	.038*
3	INCA™ Actual, Log10	.19	-.78	-1.92 to .36	.180
4	Doses Used Rate	.19	-.78	-1.99 to .43	.204
	Self-reported Adherence				
5	MMAS Total 1 Month FU	.17	.11	-1.75 to 1.97	.904
	Prescription Refill Adherence				
6	MPR Salmeterol/Fluticasone	.19	-.43	-1.64 to .79	.488
7	PDC Salmeterol/Fluticasone	.19	-.36	-1.58 to .86	.560

Note. CAT, COPD Assessment Test; MMAS, Morisky Medication Adherence Scale; FU, follow up; INCA, Inhaler Compliance Assessment; MPR, Medication Possession Ratio; PDC, Proportion of Days Covered. Adjusted for baseline CAT.

* Significant at the 0.05 level

Table 5. Ordinal logistic regression models predicting scores on the MRC Dyspnoea scale at one-month follow-up. Models were adjusted for baseline MRC score.

Model Number	Variable	Odds Ratio	95% CI	*p* value
	INCA™ Adherence			
1	INCA™ Attempted	.77	.57 to 1.04	.093
2	INCA™ Attempted Interval	.81	.61 to 1.09	.164
3	INCA™ Actual, Log10	.92	.69 to 1.23	.586
4	Doses Used Rate	.72	.52 to .99	.043*
	Self-reported Adherence			
5	MMAS Total 1 Month FU	.82	.57 to 1.18	.279
	Prescription Refill Adherence			
6	MPR Salmeterol/Fluticasone	1.05	.77 to 1.43	.768
7	PDC Salmeterol/Fluticasone	1.05	.77 to 1.43	.735

Note. MRC, Medical Research Council; MMAS, Morisky Medication Adherence Scale; FU, follow up; INCA, Inhaler Compliance Assessment; MPR, Medication Possession Ratio; PDC, Proportion of Days Covered. Adjusted for baseline MRC Dyspnoea score.

* Significant at the 0.05 level

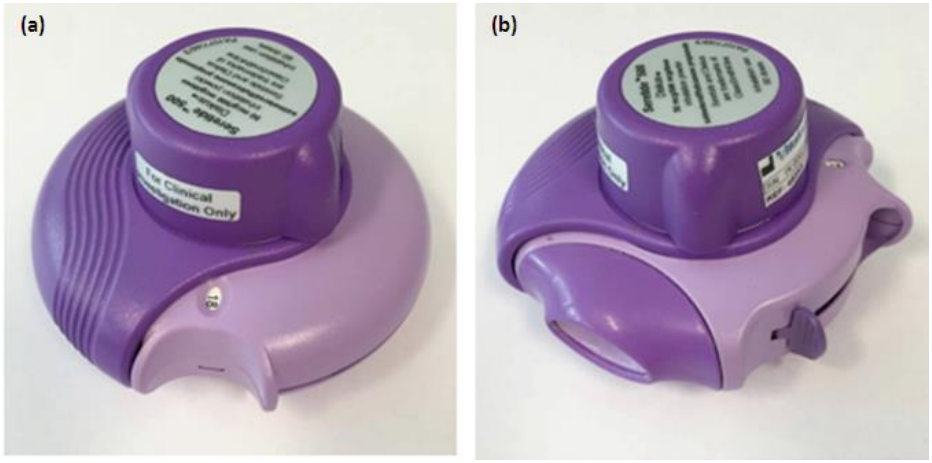

Figure 1. An image of a sample salmeterol/fluticasone Diskus™ inhaler fitted with an INCA™ device (a). Opening the inhaler initiates an audio recording to be made (b). The INCA™ is CE marked, and was designed at the Department of Bioengineering, Trinity College, the University of Dublin, Ireland and is manufactured by Vitalograph, Ennis, Ireland.

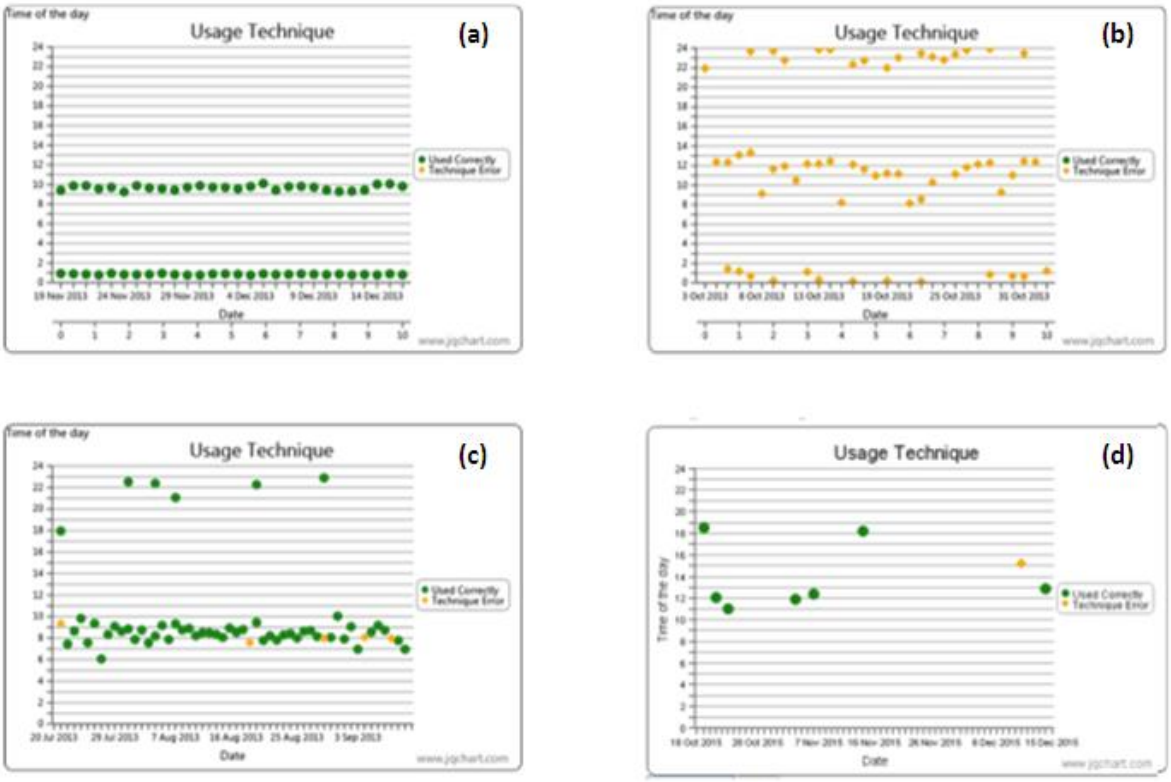

Figure 2. Patterns of inhaler technique shown by COPD patients in a preliminary study. Green dots indicate correct technique, and orange diamonds represent technique errors. In (a) the patient has the correct technique and takes the inhaler at the correct times, regularly interspersed at approximately 12-hourly intervals. In (b) the patient uses the inhaler incorrectly but takes the inhaler at the correct times, regularly interspersed at approximately 12-hourly intervals (i.e. unintentional nonadherence). In (c) the patient usually takes the inhaler correctly but only once a day. In (d) the patient rarely used their inhaler (i.e. intentional nonadherence).

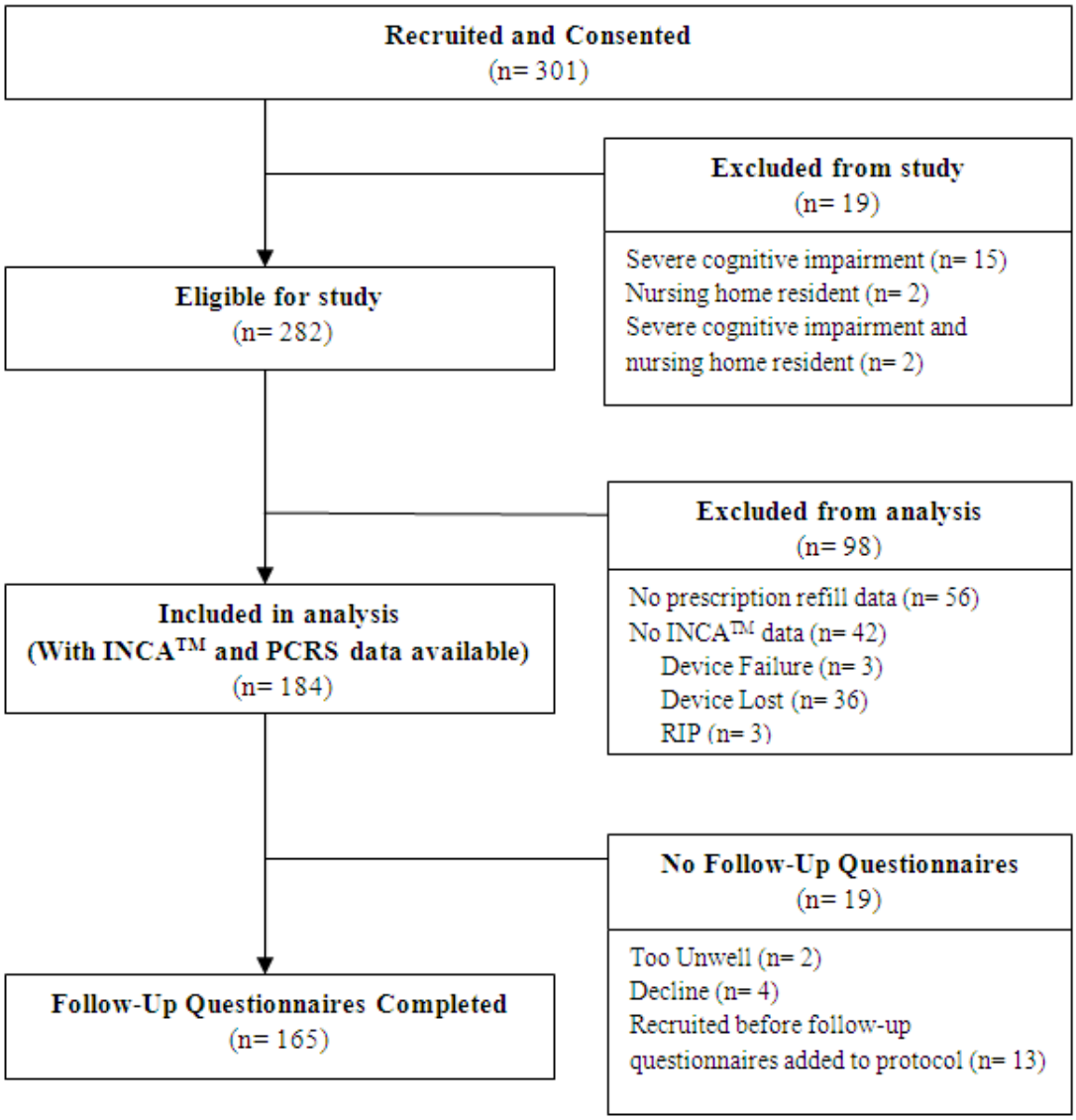

Figure 3. Consort diagram detailing study participation.

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