MONITORING NEBULISER USAGE & LUNG FUNCTION IN CLINICAL TRIALS

Adherence levels to inhalation treatments are known to be generally low. This issue is particularly important when testing nebulised drugs in clinical trials, since efficacy and safety cannot be properly evaluated otherwise. Carola Fuchs, PhD, Program Manager e-Health, and Yvonne Koehler, Study Manager e-Health, both of PARI Group, explain how PARI's special eTrack® Controller – part of the eFlow® nebuliser platform – can be used to monitor adherence during inhalation therapy which facilitates objective and remote monitoring.

In addition to efficacious drugs and efficient delivery systems, adherence to inhalation treatments is important to get the best result from respiratory therapies.[1]

It is known that adherence to everyday therapy for chronic conditions is generally low with an average of about 50%. This is also true for nebulisation therapy.[2]

It is therefore important to get accurate information about adherence. Electronic nebulisers are a good way of obtaining objective data about adherence – with an adherence average of 36%, they generally show lower adherence levels than those evaluated from diaries, medication consumption or estimation by study nurses.[3]

In clinical trials of new drug candidates for nebulisers, adherence is especially relevant to ensure that the efficacy and safety of a certain inhaled drug dose is evaluated and maintained correctly. Adherence is an important control factor in clinical trials even though adherence rates are generally higher than in everyday therapy.

In one review, non-adherence to treatment protocol was reported in 98% of trials analysed for adherence issues. However, reporting on non-adherence is often vague or incomplete.[4]

In numerous studies, data have been analysed from clinical trials leading to the conclusion that adherence reporting is often inconsistent, resulting in biased data analyses.[5]

Osterberg reviewed 45 trials in 2005 and found that only 21 analysed adherence. The majority of those trials used unreliable methods to ascertain participant adherence, such as counting pills (11 trials) or questioning the participant in some manner (10 trials).[6]

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Figure 1: eFlow® Nebuliser System with eTrack® Controller can be used for adherence monitoring.

There is a need for more appropriate methods to adjust for any departures from treatment protocol. In addition, guidance is needed on how to choose the relevant patient group for analysis of outcomes in the presence of such non-adherence, as well as corresponding considerations in the study protocol.

The impact of non-adherence on the cost of studies is immense. Higher rates of non-adherence compromise the significance of the outcome and, in turn, necessitate higher numbers of participating patients. A non-adherence rate of 30% results in a 50% increase of the necessary sample size and a 50% non-adherence rate necessitates a sample size increase of 200%.[7]

PARI Pharma GmbH, an affiliate of PARI Medical Holding GmbH, has developed the special eTrack® Controller (eTrack®) as part of the eFlow® nebuliser platform to monitor adherence during inhalation therapy which facilitates objective and remote monitoring on the PARItrack® web portal.

The eTrack® is already in use by more than 1,000 patients and has been proven to be beneficial in several multi-centre clinical trials performed by different pharma partners for different indications.

eTRACK® & PARItrack®

eFlow® technology nebulisers are based on PARI's proprietary vibrating membrane technology. These nebulisers offer short treatment times, are portable (battery operated) and virtually silent. They are used for the development and subsequent commercialisation of many drug products which need to be administered as a fine aerosol directly to the lungs of patients. PARI Pharma GmbH out-licenses its eFlow nebuliser platforms and has entered into close collaboration with pharmaceutical companies to develop drug/device combination products utilising customised eFlow® technology nebulisers.[8]

In order to objectively measure adherence to inhaled therapies that are administered via an eFlow® technology nebuliser, PARI has incorporated Bluetooth wireless technology and storage capacity on the circuit board of a special eFlow® control unit called eTrack® Controller (Figure 1). These features allow for data transfer from the device.

The eTrack® can operate all of the available eFlow® nebuliser handsets, including the eFlow® rapid nebuliser handset and a range of customised, drug-specific handsets.

Data on date, time and duration of nebulisation as well as end of nebulisation criteria are recorded for each nebulisation event. An option is included to select and transmit the name of the administered drug.

After each inhalation treatment, the locally stored nebulisation data are encrypted and automatically transferred via Bluetooth to a 2net™ Hub (Qualcomm Life, San Diego, CA, US). The 2net™ Hub transmits the data via GSM to Qualcomm's cloud from where it is sent to PARI's central server (Figure 2).

The data can be accessed remotely via a web portal called PARItrack® which has been specifically developed for use in clinical trials in compliance with the applicable data protection regulations. Study investigator and study personnel can access the relevant patient use data, depending on their access rights. Access to and evaluation of the data can be adjusted to suit the needs of each individual clinical trial.

PARItrack® contains a dashboard that provides an overview of the adherence of all patients participating in the clinical trial. This dashboard enables the notifications for low adherence to be defined for each individual. It also summarises high level

Figure 2: Set-up of data transfer from eTrack® Controller to PARItrack® web portal.

information on the number of patients and average overall adherence rates as well as average adherence rates for a recent period (e.g. the last few days). Notifications on the PARItrack® dashboard allow easy data access and highlight individuals that might need to be contacted directly to provide assistance with any issues they may encounter or to remind them to adhere to their therapy.

The levels of notifications are study specific and can be set up and adjusted by the primary investigator.

Besides the dashboard, each patient inhalation dataset can be reviewed including details on time stamp, duration and switch-off criteria. Additionally, the adherence of each patient over a selected time period can be visualised graphically for easy evaluation.

If needed, the system can be adjusted to define the validity of a treatment session with respect to a minimum duration of nebulisation and the time interval between treatments, depending on the study protocol.

RESULTS ON ADHERENCE MONITORING

The eTrack® and PARItrack® have already been used in several clinical trials in Europe, the US and Canada.

Table 1 gives an overview of clinical trials of inhaled drug products that used eTrack® and PARItrack® or former versions of the system to monitor adherence and shows the corresponding adherence rates within each study.

The results show that a very high level of adherence can be realised if the study protocol instructs that the system is used to intervene directly in cases of non-adherence. Two studies (Studies 1 and 2 from Table 1) achieved average adherence rates of 98% and 96%, with adherence ranging from 82% to 100% and 64% to 100%, respectively for daily inhalations over periods of four and six weeks with daily remote monitoring and intervention as needed. Most patients were completely adherent and only very few patients had low adherence.

The very high adherence rates of Study 2 were sufficient for analysing the efficacy of the drug under investigation even in a small group of only ten patients. To increase the significance of the results, a sub-group analysis of all patients with an adherence rate of minimum 95% was possible.

Another study, which focussed on cystic fibrosis patients with a four-week treatment phase and a cross-over design with the control arm (Study 3), had the same high adherence rates even in the absence of direct intervention in case of non-adherence. Just the awareness by the patients that they were being monitored resulted in very high levels of adherence. Mean adherence was 99% (range 82–100%) for all patients and there was no significant difference between paediatric patients of 7–13 years of age with an adherence of 99% (range 87–100%) and the older patients (>13 years age) with an average adherence rate of 98% (range 82–100%). The adherence rate was comparable in all treatment cycles, independent of whether the patient was randomised to receive the investigational drug product within the first or the second treatment cycle.

The mean adherence rate in both studies with two prescribed daily inhalations over longer periods of six months and two years, respectively, still averaged 76% (Studies 5 and 6). This level of adherence was achieved even though the therapy was for prophylaxis and did not result in any immediate relief of symptoms.

> "The remote, automatic evaluation of therapy adherence and monitoring of lung function at home using the PARI devices is more convenient and more reliable than data collection from patient diaries."

For clinical trials lasting from six months to two years, the adherence rate decreased over time as already observed by Griese.[11] In the first month of Study 6, average adherence was 78% and decreased to 71% for the last three months.

This study also enabled a comparison to be made between using an electronic nebuliser and counting drug vials to evaluate adherence. The average adherence for the electronic nebuliser was 76% measured objectively over the whole study period, whereas the adherence calculated from counting drug vials was 88%, which underscores the need for an objective method.

Figure 3 shows a graphical adherence report of one patient (upper graph) and an overview of adherence of all patients within Study 4 (lower graph). The first report shows daily adherence (purple bars) and cumulative adherence (blue line) over

Study	Indication (category of active component)	Intervention in case of non-adherence [yes/no]	Duration of study	Number of treatments per day	Number of patients*	Mean adherence (range) [%]
1	COPD (anti-inflammatory)[9]	yes	2 x 4 weeks	1	40	98 (82-100)
2	Undisclosed	yes	6 weeks	2	10	96 (64-100)
3	Cystic fibrosis (antibiotic)[10]	no	4 weeks	2	54	99 (82-100)
4	Undisclosed	yes**	4 weeks	2	40	96 (60-100)
5	Prevention of chronic transplant rejection by patients following lung transplantation (immunosuppressive drug)	yes**	2 years	2	120	76 (10-100)
6	Cystic fibrosis (anti-inflammatory)[11]	no	24 weeks	2	35	76 (20-100)

Table 1: Overview of clinical studies using eTrack® and PARItrack® for adherence monitoring. *Withdrawn patients were not considered for adherence calculation **Intervention regarding adherence was only done at patients' visits in the clinic

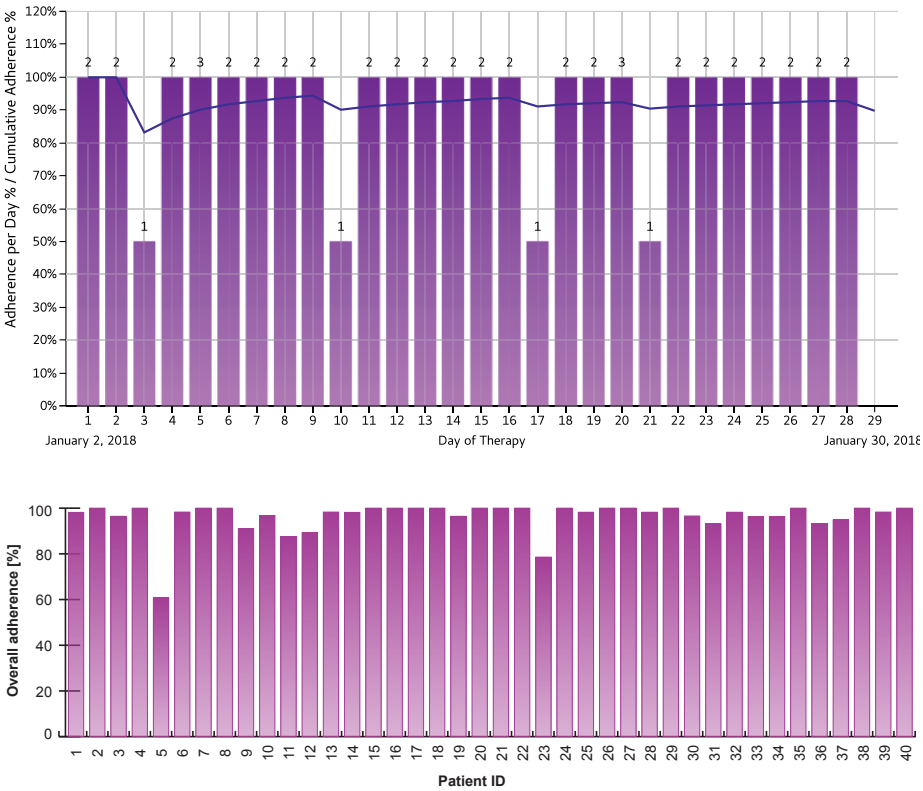

Figure 3: Graphical display of adherence rates: adherence report of a single patient over a selected therapy period (top) and overview of adherence of all patients within Study 4 (bottom).

the selected period. Within this period the patient was fully adherent on most days. On four days the patient only administered one instead of two inhalations, resulting in an overall adherence in the displayed period of 90%. The second report shows that overall adherence of most patients in this study was above 95% and only very few had a considerably lower adherence rate. This may allow the investigator to select only the most adherent patients for the evaluation of drug efficacy and safety.

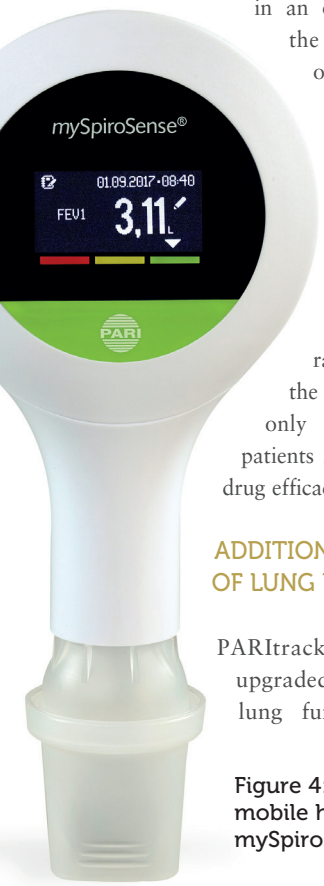

Figure 4: PARI's connected mobile home spirometer mySpirosense® Track.

ADDITIONAL MONITORING OF LUNG FUNCTION

PARItrack® was recently upgraded to also monitor lung function of patients with a Bluetooth-enabled mobile spirometer. This enables integration of the SpiroSense® spirometry solution from PARI GmbH into the digital platform by way of a new version called mySpiroSense® Track (Figure 4).

The spirometer uses hot wire anemometry and does not require the patient to calibrate the device. It is developed for paediatric and adult patients and especially designed for use in the home setting. Each home measurement provides lung function parameters and the entire flow-volume curve. All data is stored on the device and automatically transferred via Bluetooth to the 2net™ Hub and via cloud to the server corresponding to the setup in Figure 2. The remote availability of the flow-volume curve allows the physician to verify the validity of the breathing manoeuvre for each measurement, which is especially critical for home spirometry.

This new feature enables both therapy adherence and lung function to be monitored during any clinical studies based on the corresponding study protocol. eTrack® and mySpiroSense® Track are both paired to the same hub and may be given to the patient at different time points depending on the individual treatment plan or individual study protocol. A graphical evaluation of adherence to therapy and lung function of a typical patient is shown in Figure 5.

The study personnel, investigators or physicians can interpret the combination of adherence and lung function easily on the basis of the displayed graphs.

For the spirometer data, study-specific notifications can also be implemented.

SUMMARY

The remote, automatic evaluation of therapy adherence and monitoring of lung function at home using the PARI devices is more convenient and more reliable than data collection from patient diaries. In addition, remote monitoring allows for immediate intervention. The system can

Figure 5: PARItrack® enables remote monitoring of both lung function and adherence to therapy.

also be used in multi-centre studies; local site personnel can receive limited access to those patients just at their site, while investigators and personnel responsible for the overall study can analyse the overall patient group.

Site-specific adherence rates of all patients within one site in comparison to all sites can trigger site-specific training or customised notifications focused on non-adherent patients.

Monitoring both adherence and lung function are highly valuable for the interpretation of outcomes on clinical endpoints and may enhance the significance of efficacy and safety data, thus reducing the number of patients to be enrolled and the costs of the study. Linking potential side effects or adverse events to adherence may also help to identify potential correlations.

The monitoring feature offers the potential to trace the causes of observed treatment failure, which may, for example, be due to a lack of efficacy of a drug or non-adherence of a patient to the prescribed treatment regimen.

The high adherence rates achieved in the aforementioned trials demonstrate the utility and benefit of remote monitoring and immediate intervention to achieve good adherence and valuable results in a clinical trial.

OUTLOOK

In future, the infrastructure of PARItrack® may be extended with an app which will enable patients to access all their collected data and help them to improve adherence by using motivational reminders. The app could also be used to process questionnaires. For example, patient-reported outcome questionnaires are moving into the focus of clinical trials and could be controlled via an app linked to the web portal.[12]

Monitoring features of health status and adherence should be used in clinical trials and should then be transferred into patient-centred care management solutions for chronically ill patients. Improving adherence to long-term regimens requires:

- A combination of information about the disease and therapy
- Counselling about the importance of adherence and on how to organise the administration of medication
- Reminders about appointments and adherence
- Rewards and recognition for the patient's efforts to follow the regimen
- The enlisting of social support from family and friends.

Successful interventions for long-term regimens are all labour intensive, but can ultimately enhance outcomes and be cost-effective.[13]

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