

WHITE PAPER



Adherence in Asthma: Comparing Clinical Trials to the “Real-World”

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EXECUTIVE SUMMARY

Inadequate medication adherence is a widespread issue with an estimated annual cost to the healthcare system between \$100 billion and \$289 billion in the US and €125 billion in the European Union.

In asthma clinical trials, rates of adherence are typically high and often exceed 90% with one reporting ≥96% adherence over a 52 week period. However this is not uniform finding and in a long term placebo controlled trial of an inhaled steroid in children, where participants were not informed that adherence was being monitored, after 27 months, adherence with the inhaled steroid was <50% and with placebo 32%. Thus, the lengths of the clinical trial, the patient population, knowledge of monitoring and other factors are always likely to have a significant effect in trial adherence.

In the 'real-world', studies across a range of disease severities have consistently reported significant rates of non-adherence despite a direct correlation between medication intake and patient-reported symptom improvement or negative outcomes.

Non-adherence can significantly affect both efficacy and safety results. Uncertainty in this area prompts questions, such as if the study drug has limited or no effect, is it because the patient population was poorly adherent in the recruitment / screening period, the investigational drug or dose is inadequate to demonstrate efficacy or that the adherence investigational drug is low? This issue therefore affects multiple stakeholders including pharmaceutical companies, regulators, prescribers, payors and patients.

In this paper we offer practical solutions to these issues. We address the strengths and limitations of different methods of measuring adherence in clinical trials, the effect of non-adherence on clinical trial outcomes and possible regulatory implications. Importantly, we then address the issue of understanding the differences in adherence in clinical trials and the real-world setting and therefore the different methods of measuring adherence. Finally, we close by looking to the future and addressing the changing environment of real-world studies.

INTRODUCTION

Inadequate medication adherence is a widespread issue with an estimated annual cost to the healthcare system between \$100 billion and \$289 billion in the US¹ and €125 billion in the European Union.² Long-term adherence to medication is particularly challenging for patients, and an estimated 50% of prescriptions filled for chronic diseases are not taken as prescribed.¹ Numerous studies have examined barriers to adherence, and findings indicate that the problem is multidimensional and influenced by a complex interplay of five factors³:

- Social/economic (e.g., poverty, limited education, cultural beliefs, stigma, lack of support systems)
- Healthcare team/system (e.g., provider-patient relationship, insurance, level of available health services)
- Condition/disease (e.g., severity of symptoms, level of disability, comorbidities)
- Therapy (e.g., regimen complexity and convenience [including dosing frequency and dosage form], side effects, immediate vs. delayed benefit, convenience)
- Patient (e.g., knowledge and beliefs about disease, low expectations for treatment efficacy, concern regarding side effects, lack of motivation and limited confidence in ability to manage condition).

Many of these factors result in “non-intentional non-adherence,” whereby the patient wishes to take medication as prescribed but practical barriers prevent them from doing so. However, other factors involve patient decision making and behavior and present perceptual barriers to medication adherence. Thus, addressing non-adherence in a ‘real-world’ clinical setting requires a patient focused ‘menu driven’ approach which identifies the underlying reason for sub-optimal adherence.

In asthma clinical trials, rates of adherence are typically high and often exceed 90% with one reporting $\geq 96\%$ adherence over a 52 week period.^{4,5,6} However, this is not uniform finding and in a long term placebo controlled trial of an inhaled steroid in children, where participants were not informed that adherence was being monitored, after 27 months adherence with the inhaled steroid was $< 50\%$ and with placebo 32%⁷. Thus, the length of the clinical trial, the patient population, knowledge of monitoring and other factors are always likely to have a significant effect in trial adherence – bottom line, adherence in asthma studies needs to be measured and measured accurately to interpret outcomes in clinical trials.

In real-world settings, studies across a range of disease severities have consistently reported significant rates of non-adherence despite a direct correlation between medication intake and patient-reported symptom improvement or negative outcomes.^{8,9,10,11} This difference, along with the inherent difficulties of accurately measuring adherence, makes it challenging to generalize the results of clinical trials to a clinical practice setting, causing uncertainty among pharmaceutical companies, regulators, prescribers, payors and patients.

The following questions need to be addressed:

- How accurate are the methods used to evaluate adherence in clinical trials?
- Can we make confident data-driven decisions to progress compounds without understanding adherence in Phase II/IIb?
- Does a low incidence of adverse events in a clinical trial indicate a well-tolerated study drug or reflect high rates of non-adherence?
- How much adherence is enough? If the study drug is successful in a clinical trial, will real-world adherence rates be high enough to demonstrate benefit in the general asthma population?
- How reliable is health economic modeling in the face of poor levels of adherence in the real-world?

This paper explores adherence to asthma medication in both clinical trials and the ‘real- world’, including measurement of adherence, data interpretation, regulatory implications and the challenges of generalizing study data to routine clinical practice.

MEASURING ADHERENCE IN CLINICAL TRIALS

There are many ways to measure adherence, but no single method provides results that are accurate, objective and cost-effective; each approach has strengths and limitations (Table 1).

Directly observed therapy (DOT) is the gold standard for measuring adherence.¹² For drugs requiring parenteral dosing, including many of the novel biologic agents in development for asthma, the need for administration by a healthcare professional provides the ideal way to capture adherence data. However, it is important to note that many of these new treatments are “add-on” therapies to standard care with high-dose inhaled therapy and adherence to these therapies is often not captured in these clinical trials. DOT for self-administered medications has traditionally required site staff to visit the patient, or the patient to visit the center; in either case this approach is time consuming and extremely inconvenient and costly, such that it is not feasible in a clinical trial setting.

In recent years, more widespread availability of the Internet and home computers has made it possible to perform DOT using technologies such as webcams. Whilst this can be implemented for specific small-

scale studies, it is not a practical solution to implement across an entire development program. Many Phase III clinical trials include centers in less developed regions, where the technological infrastructure (nationally and within the home) is not available. Whilst the cost and availability of any required hardware has reduced in recent years, the cost and logistics still limit the potential to implement these on a large scale. If webcam-based DOT is planned, this needs to be decided at an early stage and factored into the country selection process. Examples of where this approach has been successfully utilized include pediatric hypothalamic-pituitary-adrenal (HPA) studies or knemometry studies for inhaled corticosteroids.

Despite the limitations of patient recall/surveys, pill counts, dose counters or weighing canisters,^{13,14,15} these methods remain the most pragmatic, and therefore the most commonly used adherence measurement techniques in clinical studies in asthma.

A usual starting point is patient self-reported data; this can be obtained verbally during the consultation or more commonly it can be obtained by asking the patient to complete a questionnaire/patient diary. Patient self-reporting has been shown to overestimate adherence compared to objective measures such as weighing canisters and electronic dose counting.^{16,17,18} In one study, median adherence using an electronic device was found to be 37.5%, compared with adherence calculated from asthma diaries of 93.1%.¹⁷

Another alternative is post-returning the inhaler device to the investigators; it can be weighed. The remaining doses are then calculated. Canister weighing has been noted to overestimate adherence when compared with electronic dose-counting devices.^{17,19,20,21}

Table 1: Strengths and limitations of adherence measurement methods

MEASUREMENT METHOD	STRENGTHS	LIMITATIONS
Directly observed therapy	<ul style="list-style-type: none"> • Gold standard • Digital solutions (e.g., webcam) provide a permanent record with a time and date stamp 	<ul style="list-style-type: none"> • Cost of staff to monitor therapy (in the clinic, at the patient's home, over the internet, etc.) • For digital solutions, cost of the technology infrastructure and its accessibility to patients • Inconvenient for patients
Patient recall*	<ul style="list-style-type: none"> • Fast • Easy 	<ul style="list-style-type: none"> • Requires patients to remember and report accurately
Patient surveys	<ul style="list-style-type: none"> • Low cost • Easy • Requires little provider time 	<ul style="list-style-type: none"> • Requires patients to remember and report accurately • May not be validated in severe asthma
Patient diaries (paper or electronic)	<ul style="list-style-type: none"> • Low cost • Requires little provider time • Many electronic diaries can be programmed to remind the patient to take their medication • Electronic methods provide date and time stamps for data entry 	<ul style="list-style-type: none"> • Requires patient adherence to both medication and record-keeping • Patients may return inaccurate paper-based diaries in an effort to please the provider, making the data generally inadequate for pivotal submission studies
Pill counts/inhaled dose counters/ weighing canisters	<ul style="list-style-type: none"> • Easy to train site staff to perform • Provides an objective measurement • Relatively fast (dose counters) 	<ul style="list-style-type: none"> • Patients must remember to bring prescription bottles/inhalers to clinic visits • Requires provider time to count the pills or weigh canister • Affected by dose dumping
Prescription refill rates	<ul style="list-style-type: none"> • Provides maximum possible adherence rates (patients can't take medication they don't have) • Reasonably easy to obtain data during a clinical trial 	<ul style="list-style-type: none"> • Refilling a prescription does not necessarily mean that the patient is taking the medicine

Table 1: Strengths and limitations of adherence measurement methods (continued)

MEASUREMENT METHOD	STRENGTHS	LIMITATIONS
Electronic monitoring [†]	<ul style="list-style-type: none"> • Accurate (time and date stamped) • No additional effort required from patient 	<ul style="list-style-type: none"> • Expensive • Relies on the assumption that the patient actually took the medicine and did not just open the pill bottle or discharge the inhaler • For real-world studies presence of the device may alter behavior and artificially increase adherence
Drug assays (pharmacokinetics)	<ul style="list-style-type: none"> • Accurate • Reasonably low cost • Cannot be directly manipulated by patient • Requires very little provider time 	<ul style="list-style-type: none"> • Only indicates adherence just before a clinic visit • Patients may be reluctant to undergo blood draws • If other blood samples are not required by the study, collection requires an additional procedure with an incremental cost
Disease-specific surrogate markers	<ul style="list-style-type: none"> • Accurate (once validated) • Cannot be manipulated by patient • Monitoring may be part of routine care 	<ul style="list-style-type: none"> • Tests may be expensive if outside of routine care • Appropriate surrogate markers have not been identified for all diseases • Primary value is during a run-in period
Biomarkers	<ul style="list-style-type: none"> • Accurate • Cannot be directly manipulated by patient • Requires very little provider time 	<ul style="list-style-type: none"> • Expensive • Conflicting data regarding the utility of many biomarkers • Some biomarkers may be influenced by adherence just before clinic visit • Patients may be reluctant to undergo blood draws • If other blood samples are not required by the study, collection requires an additional procedure with an incremental cost • Primary value is during a run-in period

**Patient response to an open-ended question, such as, “In the last week, how many days did you take your medicine?”*

†For example, electronic pill boxes, sensors in pill bottle caps or devices attached to inhalers that record the date and time each time they are activated

This may, in part, be due to use of the device to test if it is functioning and to “dose dumping,” in which the inhaler is discharged several times into the air at one sitting in order to give the impression of improved adherence.^{17,19,20} A study carried out by a compliance working group attempted to address this by omitting the electronic data from the first and last days of the study period as it was felt that these would be the days in which dumping was most likely to occur.¹⁷ An alternative study found comparable findings, and the overestimation of adherence obtained by canister weighing was attributed to actuations discharged in a non-prescribed manner, as only two of several actuations at any one sitting would be counted by the electronic device.²⁰

Electronic monitoring devices, including time/date recorders on pill bottles or attachments to inhaler devices, have been available for some time, and these can provide very high quality information on adherence rates; these have not been widely implemented in industry research. One of the reasons for this is that pivotal registration studies should normally be conducted using a final formulation of the drug product, and any adherence monitoring device added onto an inhaler that would not be part of the final drug product may introduce further regulatory hurdles.

These techniques have their challenges. They give no information about whether the doses were actually inhaled or were simply discharged. They are also relatively expensive methods of monitoring medication use. One study reported that a number of subjects had used the inhaler occasionally over the course of the study period without the device attached.²² Data retrieval issues have been cited as being problems with the devices, as has battery failure.^{17,20,23} In a large study, 380 (20%) of 2360 downloads failed; this was attributed to failure of device or battery and the proximity during use to other magnets or batteries.²³

Use of oral medication such as theophylline or oral corticosteroids (OCS) can also be monitored electronically, using devices which record the date and times of pill-bottle opening and closing.^{21,24} This suffers from the drawback that no information is given about how many pills were removed at a time, or whether or not they were taken. It can give some insight into dose dumping. In one study, 37 bottle openings were recorded by two patients in a two-minute period.²⁴

Use of electronic patient diaries that record if adherence data was entered within an allocated time window is increasing. This approach may represent the optimal balance between pragmatism and confidence in the adherence data. The more cautious individuals would still point out that this relies on the assumption that compliance with data recording correlates to actually taking the medication.

EFFECT OF NON-ADHERENCE ON CLINICAL TRIAL OUTCOMES

In clinical trials, non-adherence can significantly affect both efficacy and safety results. Uncertainly in this area prompts questions, such as:

- If the study drug has limited or no effect, is it because:
 - the patient population was poorly adherent in the recruitment / screening period and adherence is improved in the placebo arm during closer monitoring in the trial (the “Hawthorne effect”)
 - the IMP drug/dose is inadequate to demonstrate efficacy
 - or that the adherence is low to the IMP.
- If there are few study drug-related adverse events, is it because the drug is safe or because the trial participants are not taking it?

This issue becomes increasingly complex in trials involving patients with more severe disease who are using the investigational drug as “add-on” therapy to background medication, particularly if the rates of adherence differ by regimen component (Table 2). Since adherence to background therapy is rarely measured, it can be difficult to unravel the relative contributions of the study drug and background medication to clinical trial outcomes.

Uncertainty about adherence to background therapy is further complicated by the possibility of a change in adherence to background medication at screening or randomisation. This is particularly relevant in asthma where asthma severity is defined by failure to respond to certain defined levels of treatment. Typically in asthma studies, the “severity” of the intended asthma population is defined by structuring the core inclusion and exclusion criteria around the patient’s therapy at baseline and baseline exacerbation rates in the previous year or symptoms control whilst taking this baseline therapy. This allows the overall study population to be correlated with a GINA treatment step where the drug is likely to be used and around which a licensing application is likely to be based.

Patients who appear uncontrolled at the screening visit may simply be uncontrolled due to non-adherence with their existing therapy, and they may not actually require a “step-up” in treatment. Patients in all treatment arms, including placebo may improve if adherence with background medication increases significantly, and any room for improvement between placebo and the add-on therapy under evaluation can be reduced or even eliminated. As an example of this challenge, current novel biologics in asthma have been targeted at patients with severe asthma which is primarily defined as persistent Th2 / eosinophilic inflammation despite high dose inhaled steroid treatment. This is either defined by blood / sputum eosinophilia or other biomarkers of persistent Th2 signaling e.g. periostin. However, one of the recent adherence

studies in this population demonstrated that patients with low prescription filling for inhaled steroid therapy had higher sputum eosinophils than patients with regular prescription filling (sputum eosinophil count $4.6 \pm 0.7\%$ v $2.3 \pm 0.5\%$, $p = 0.05$). There is an inherent challenge in ensuring that the patient population being studied is adherent with the prescribed level of therapy and ensuring that the population has a persistent Th2 / eosinophilic inflammation despite high dose inhaled steroid treatment. Novel strategies for identifying non-adherence in severe asthma in the clinic setting, for example defining short-term responses of Th2 biomarkers to directly inhaled steroid observed therapy, may provide more objective assessments of patient populations recruited to these studies and could easily be employed in the run-in period of clinical trials requiring patients who incompletely respond to high dose inhaled steroid therapy.²⁵

The typical mechanism to try and mitigate the risk of non-adherence influencing the recruited patient population in asthma clinical trials is to include a run-in period, as it has been believed that patients who change their behavior as a result of inclusion in the trial are likely to do so immediately after the screening visit. In others, the provision of the background medication free of charge during the run-in may also reduce the barriers to adherence. Ideally, the duration of the run-in period should be adequate for the mechanism of action of the background medication, for example, an inhaled corticosteroid (ICS) therapy takes longer to demonstrate efficacy than a long-acting β -agonist (LABA). By introducing a re-evaluation of key severity criteria at the end of the run-in period, formerly non-adherent patients with improved lung function or symptoms scores may no longer meet the entry criteria for the trial and can be excluded. While this approach is likely to lead to an increase in the number of “run-in failures” and may lengthen the time needed to enroll the study, this disadvantage is probably outweighed by the increased confidence that the study drug has been evaluated in the most appropriate population. How-

Table 2: Effect of adherence on clinical trial outcomes

ADHERENCE TO BACKGROUND THERAPY	ADHERENCE TO STUDY DRUG	EFFICACY OUTCOMES	SAFETY OUTCOMES
Low	Low	<ul style="list-style-type: none"> No difference between the study drug and placebo groups 	<ul style="list-style-type: none"> With no active drugs on board, the incidence of drug-related adverse events may be underestimated In the absence of treatment, adverse events associated with uncontrolled disease may be overestimated and incorrectly attributed to the study drug
Low	High	<ul style="list-style-type: none"> Magnitude of combined treatment effect will be underestimated with only one component taken May overestimate the value of the study drug if intended for use solely as an 'add-on' therapy May overestimate placebo effect as background adherence to "baseline" medication improves during clinical trial 	<ul style="list-style-type: none"> Potential drug-drug interactions between treatments intended for co-administration may not be detected
High	Low	<ul style="list-style-type: none"> No difference between the study drug and placebo groups 	<ul style="list-style-type: none"> Without the study drug on board, the incidence of drug-related adverse events may be underestimated Potential drug-drug interactions between treatments intended for co-administration may not be detected
High	High	<ul style="list-style-type: none"> Most accurate assessment of study drug 	<ul style="list-style-type: none"> Most accurate assessment of study drug

ever, longer term criteria such as “historical” exacerbation frequency will not be affected by an improvement in short-term adherence and if this is a key inclusion criterion, which is effectively driven by non-adherence, it becomes very challenging to recruit this population.

Conversely, adherence to background medications in previously adherent patients may wane during the study if the patient decides that the background regimen is no longer needed. This impetus for this decision may be particularly strong in patients who:

- are deriving significant benefit from the investigational drug (they “feel better”)
- have concerns about the adverse events and/or long-term safety associated with their existing medications (e.g., maintenance oral corticosteroid therapy)
- suffer from treatment fatigue
- pay for their own background medication.

Clearly, incomplete adherence to background therapy is likely to affect outcomes, and failure to address these issues at the time of the study allows only speculative assessments of potential treatment interactions. One example is the pooled safety data on asthma-related hospitalizations that was presented to the pulmonary allergy division of the FDA in 2008.²⁶ While the underlying mechanisms around LABAs and serious adverse asthma-related outcomes are not well understood, it is widely suspected that any risk is conferred by the absence of adequate anti-inflammatory therapy. In patients randomized to a LABA added to a background ICS regimen versus a background ICS regimen alone, the risk difference for asthma-related hospitalizations was 46.02/10,000 patients (95% CI: 8.10 to 83.93). In comparison, in patients randomized to LABA and ICS (both provided, but as separate medications), the risk difference decreased to 14.48/10,000 patients and was no longer statistically significant (95% CI: -30.83 to 59.79). The most logical reason for this result was higher rates of adherence in studies that supplied patients with both medications. Furthermore, when the LABA

and ICS were provided as a combination product (thus eliminating the possibility of an adherence differential between components), the risk difference between LABA/ICS and ICS alone was negligible (0.28/10,000 patients; 95% CI: -18.51 to 19.06). While this example is somewhat extreme, it demonstrates how failure to understand adherence patterns can lead to changes to the drug label, require additional investment in clinical studies and cause uncertainty in the medical and scientific communities.

REGULATORY IMPLICATIONS

Submission

The implications of failure to demonstrate efficacy in a pivotal trial are clear: the sponsor will be required to perform additional studies, which is highly likely to delay submission and approval timelines. The sponsor will also need to explain why the study or the study drug failed, and the regulators will need to be satisfied with any explanation for unexpected, discrepant data.

The relationship between medication adherence and safety outcomes presents a slightly different challenge, particularly in longer-term (≥ 1 year) studies. Such trials may be randomized, blinded and carefully controlled, but they are not uncommonly open label, often using standard of care as the control arm. Placebo controls are usually avoided in long-term studies because of ethical concerns about patients receiving inadequate treatment for a significant length of time. Ethical concerns may also prohibit the inclusion of a positive control for endpoints, for example, growth or HPA axis suppression in children. In the absence of placebo or a positive control, regulatory agencies may demand greater assurance that the absence of a safety finding is not simply due to non-adherence with the active medication. The text below is from a regulatory assessor review of a pivotal safety study for a new novel compound’s drug application delivered via metered

dose inhaler. It illustrates the scrutiny that assessors may place on the methodology for assessing adherence in this setting:

Compliance was assessed by the patient's notation in the diary that the medication was taken and by weighing the returned canisters... Compliance with study medication was high: >90% compliance in >85% of the subjects in each treatment group by diary record. Compliance assessed by canister weight was slightly lower: 79.6, 81.9 and 80.4% in the [respective treatment groups]. This was attributed to errors in canister weighing procedures...

The overall validity of the study results could not be assured. The study was conducted in mild asthma patients who may or may not have required using [treatment] for the whole year. There was no difference in efficacy measures, such as FEV1, that could assure compliance. Furthermore, [drug] levels were not measured in the study.

This also highlights the potential need to gain regulatory agency “buy-in” to any proposed methods or surrogates for adherence that the sponsor may rely on.

In terms of how adherence data should be presented, there is very little guidance around this. The literature presents adherence either as a continuous variable (% of utilized medication expressed as a percentage of prescribed medication) or dichotomizes (this value with thresholds of 80% or 50% being used to define non-adherent populations). This method of analysis does not report poor adherence with dose timing or good inhaler technique and so is likely to under-report the true scale of the problem.

In clinical trials, many sponsors may define acceptable adherence as adherence of $\geq 80\%$ although others may allow a 70% or even lower threshold to allow recruitment or continuance in the clinical trial. Again in clinical trials where adherence is reported, it is usually reported as a continuous variable of % medication usage / medication prescribed and issues such as timing are

again omitted. There is no universally accepted threshold of what would constitute acceptable adherence in a clinical trial and how this should be measured or reported.

In addition, there is also no agreed method of handling missing adherence data. A study by Fitzgerald looked at the impact of increasing the dose of ICS versus no increase in ICS in patients experiencing an asthma exacerbation. When missing adherence data was entered using the patients mean adherence with ICS, this showed adherence with the intervention of >100%. This approach to handling missing data is open to criticism as non-adherence with data entry could be argued to more likely reflect non-adherence with medication: when repeating the analysis of adherence using a worst case scenario, i.e. assuming missing data reflects non-adherence, adherence was reduced by almost 20%.

Risk Mitigation Planning

It has been recognized for some time that the safety database at the time of drug approval is unlikely to be large enough to capture rare adverse events. The major regulatory agencies understand that the risk/benefit profile established during the pivotal program can be altered over time if post-licensing evidence suggests lower efficacy, if emerging data uncover new adverse events or an altered frequency of known adverse events. In addition, there is a greater awareness that a medication may be used in ways that are inconsistent with the prescription advice and product labelling and that misuse can change the risk/benefit profile of the therapy. The shift in recent time has been from a relative acceptance of these facts, to pushing sponsors to proactively address these concerns. As a result, sponsors have been required to spend more time preparing increasingly thoughtful and comprehensive risk minimization plans as part of a new drug submission package. These proposals often include methods by which the sponsor will evaluate the effectiveness of the risk mitigation plans, and studies of a drug's risk/benefit profile in a real-world setting are one way that a sponsor may choose to meet this obligation.

ADHERENCE IN REAL-WORLD SETTINGS

Several studies across a range of asthma severities have attempted to evaluate real-world adherence, consistently finding significant non-adherence despite a direct correlation between medication intake and patient-reported symptom improvement and other important clinical outcomes. For example, a study of 3373 patients with Global Initiative for Asthma (GINA)²⁷ stage 1 to 5 asthma in Nottinghamshire, UK, found that 39% of patients had filled <80% of the expected prescriptions over a 12-month period.¹¹

Some might infer that the majority of non-adherence was in patients with few symptoms who did not experience daily benefit from the medications. However, a study of 182 patients with difficult asthma (GINA step 4 or 5) in Belfast demonstrated similarly poor adherence, with 54% of patients filling $\leq 75\%$ of their prescriptions for combination inhalers over a 6-month period.⁸ The 35% of patients who filled $\leq 50\%$ of their prescriptions had significantly lower asthma-related quality-of-life scores and significantly higher usage of nebulized β -agonists compared with patients who had >50% adherence.

Again, using prescription records, at another Specialist UK Difficult Asthma service, suboptimal adherence was identified in 75 of 115 (65.2%) of patients – defined in this study as <80% filling of ICS prescriptions.⁹

The Belfast study also assessed adherence to OCS by measuring serum prednisolone and cortisol levels, amongst the 51 patients in the study who had been prescribed prednisolone (34 patients on maintenance prednisolone and 17 patients on a short rescue course). The investigators followed this up with a patient interview to discuss the concordance results.⁸ The results demonstrated that 23 of these patients (45%) were found to be non-adherent to OCS. A study carried

out at the Royal Brompton Hospital in London found similar results. Six out of eighteen patients, who were taking at least 15 mg of maintenance daily prednisolone and had demonstrated airflow reversibility, were found to have prednisolone blood levels that were undetectable with normal serum cortisol levels consistent with non-adherence.²⁸

Non-adherence to prescribed inhaled corticosteroid has also been demonstrated in children with difficult asthma referred to a UK specialist service.²⁹ This study looked at the benefits of nurse-led home visits as part of the difficult asthma protocol. The results showed that 57% of patients had picked up 80% or less of their asthma medication prescriptions and that 30% of patients had picked up less than 50% of prescriptions issued.

It is unclear why many patients appear to view asthma attacks as inevitable events to be handled as they occur rather than preventable exacerbations of an inadequately controlled medical issue.

UNDERSTANDING THE DIFFERENCES IN ADHERENCE BETWEEN CLINICAL TRIALS AND THE REAL-WORLD

The differences in adherence rates between clinical trials and the real-world are likely due to a number of overlapping and intersecting factors.

- Evidence suggests that just being included in a study with regular monitoring increases a patient's motivation to be adherent to the prescribed regimen (the Hawthorne effect³⁰).
- There is inherent selection bias in study inclusion/exclusion criteria, which usually include a stipulation

to the effect of “in the opinion of the investigator, the patient is likely to be adherent to treatment.”

There is usually no guidance on how this should be assessed or reported.

- Clinical trials may include tools, such as electronic patient diaries with alarms that prompt patients not only to enter their data but to take their medication and which are unlikely to be transferred into a real-world setting.
- Providing study medication (and sometimes background medication) free of charge may remove a barrier to adherence in patients who struggle to afford their medications.
- Medications are usually given to patients during visits to the study site instead of requiring patients to take the extra step of visiting a pharmacy.
- Some clinical trials include frequent contact between the patient and the site, which is likely to reinforce adherence.
- Methods used to measure adherence in clinical trials typically rely on patient self-reporting, which may be inaccurate and result in an overestimation of the true adherence rate.
- As part of the informed consent, patients typically receive additional education about the disease, the investigational drugs mechanism of action and the importance of adherence.

MEASURING ADHERENCE IN REAL-WORLD SETTINGS

With the acknowledged gap between medication adherence in clinical trials and the real-world, it is easy to see why payors have begun to question the value of health economic submissions that are modeled entirely on conventional clinical trial data: health economic data that is reflective of clinical practice is being regarded as increasingly relevant to address these concerns. The traditional

criticisms made of real-world pragmatic studies, which may be open-label may not be valid when evaluated from the perspective of the payor.

Paradoxically, the superior adherence in clinical trials compared to the real-world setting can also pose a challenge for pharmaceutical companies that hope to differentiate a new product based on factors such as dosing interval or patient preference, in the hope that this will lead to improved adherence in the real-world and hence improved outcomes. The artificially high adherence rate across all treatment arms in controlled clinical trials does not allow the sponsor to demonstrate that an improved device or reduced dosing interval translates into improved adherence and outcomes.

Database studies using electronic health records to expedite data extraction, are often used in real-world research (Table 3). The United Kingdom and the Netherlands are examples of countries with nationwide databases that collect a wide variety of health information from participating in-country general practitioners. US healthcare insurance datasets also act as valuable resources although they are frequently criticized for being reflective of patients with insurance rather than the general population. These existing sources of retrospective data can be analyzed quickly and relatively cheaply for a large range of diseases, including asthma.^{31,32,33,34,35,36,37,38,39} Adherence is usually estimated through a surrogate of collection of prescriptions, with very few databases capturing filling of the prescription at a pharmacy. Many other studies have explored these same issues using survey data (e.g., European Community Exploratory Health Survey⁴⁰ and datasets from a single site or group of sites).^{8,9,11}

Database studies are practical for products that are established in the marketplace for a number of years; however, their reliance on an adequate number of prescriptions over time and capturing of longitudinal data means that they are not possible options at the

time of launch when reimbursement submissions and negotiations will be taking place. This is particularly important for key health outcome endpoints such as asthma exacerbations, which are relatively infrequent events for the majority of patients.

Prospective studies are also used to assess adherence, either in an observational cohort or open-label, randomized, phase IV trial designed to mimic the clinic setting (Table 3).^{41,42,43} A good example of this is a study by Price et al who conducted two parallel, randomized, open-label multicenter trials to evaluate the real-world effectiveness of a leukotriene-receptor antagonist (LTRA). The first study compared initial maintenance treatment for asthma with either an LTRA or an inhaled glucocorticoid; the second compared LTRA or a LABA as add-on therapy in patients already receiving inhaled glucocorticoid therapy.⁴³ Both trials enrolled primary care patients 12 to 80 years of age with impaired asthma-related quality of life scores or inadequate asthma control. Contact by site staff was infrequent and most importantly, they were treated by their usual physician and they were responsible for obtaining their own medication. Adherence was measured by comparing prescriptions issued versus prescribing instructions. The study followed up on patients for two years and was able to detect differences in patterns of adherence between treatment groups, although the study was not able to detect differences in outcomes.

The most recent development in this area is the use of an unlicensed agent in a real-world clinical trial. The GSK Salford Lung Study is an ongoing, prospective, randomized, open-label trial enrolling approximately 5000 patients with asthma and 4000 patients with chronic obstructive pulmonary disease (COPD) in an underserved region in the UK.⁴⁴ Patients will receive an investigational once-daily ICS/LABA combination or standard of care for one year, and endpoints include symptoms, exacerbations, use of healthcare services and use of additional medication to control symptoms. Certain high-risk patients, including smokers, are eligible to participate.

The results of this novel study, expected in 2014, are highly anticipated by regulators, payors and the scientific community. If successful, this type of study design may be used by other products and in other therapeutic areas. If those trials also yield beneficial data, it is possible that regulators and payors will begin to expect randomized, real-world trials as part of submission packages or phase IV study commitments. However, it is important to note that GSK's investigational drug combines two established classes of medication (ICS and LABA) and has been extensively characterized in traditional clinical trials. For investigational products with less robust datasets, it may not be practical or desirable to start a real-world trial before the medication is approved.

Table 3: Opportunities and challenges of measuring adherence in a real-world setting

OPPORTUNITIES	CHALLENGES
RETROSPECTIVE STUDIES	
<ul style="list-style-type: none"> • Inexpensive compared with traditional clinical trials • Can potentially enroll large number of patients (leading to increased statistical power) • Likely to contain data on a diversity of patients, such as smokers or those with comorbid conditions 	<ul style="list-style-type: none"> • The less-structured environment for data collection may lead to questions about quality • A more limited number of outcome measures are available (than in a traditional clinical trial which can be tailored to the sponsor requirements) • Retrospective studies often use a single country database which is not compatible with datasets from other countries. This can lead to questions about the generalizability of the data to other populations • Data will not be available at launch
PROSPECTIVE STUDIES	
<ul style="list-style-type: none"> • Less costly than traditional clinical trials due to more limited interventions • Likely to contain data on a diversity of patients, such as smokers or those with comorbid conditions • Data is typically collected less frequently than in a traditional clinical trial, more closely mimicking a real-world setting 	<ul style="list-style-type: none"> • If the investigational product is commercially available, it may be difficult to avoid allocation bias in the randomization process • Requires internal confidence to instigate. The lack of control and potential for unidentified confounders to detect “false” safety or efficacy outcomes may be a barrier to internal approval

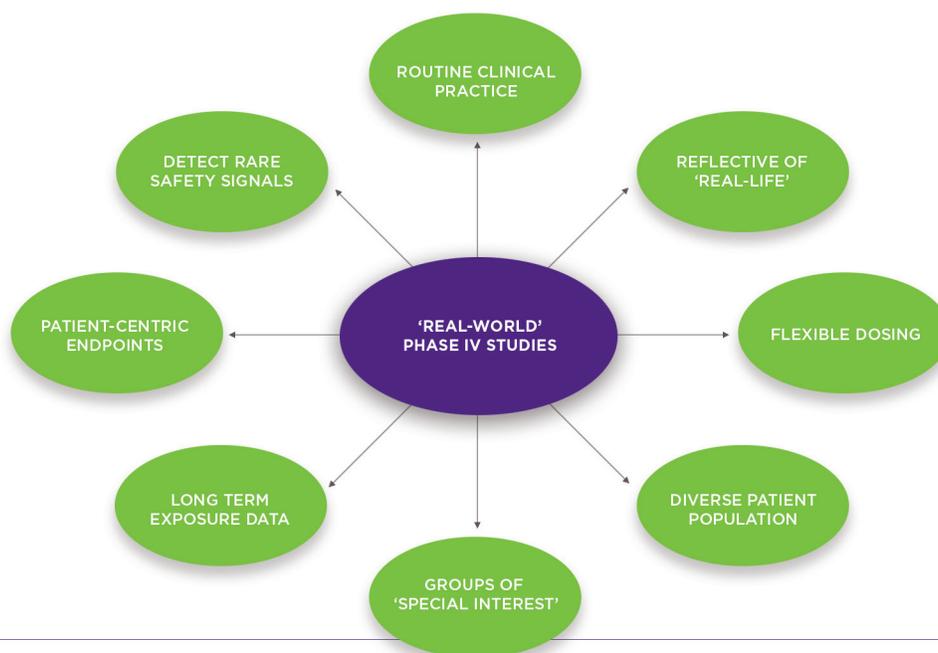


Diagram 1. The value of Phase IV, naturalistic real-world studies.

THE CHANGING ENVIRONMENT OF REAL-WORLD STUDIES

With the pharmacovigilance legislation changes in 2012 and increasing payor pressures (including value-based pricing) companies are now being challenged to plan real-world studies as part of their development programs.

Real-world studies offer companies a number of benefits in the challenging commercial environment over the traditional development program trials⁴⁵ (see diagram 1). They can be utilized to monitor safety in the real-world or naturalistic setting and may help identify safety signals that are rare or take time to develop.

Registries are becoming increasingly popular and mandated for many products in risk-management plans. Registries can include wider disease populations and are useful to confirm the safety and efficacy of products when translated into everyday clinical practice, after the drug is available for general prescribing. They can also provide supplemental safety data in patients with rare conditions. Although registry studies may at times be subject to case selection (since they are not randomized), they can produce a wealth of valuable data when properly managed. For example, they can produce long term data collection with less administrative burden of traditional trials and provide additional data on patient related outcomes and healthcare resource utilization.

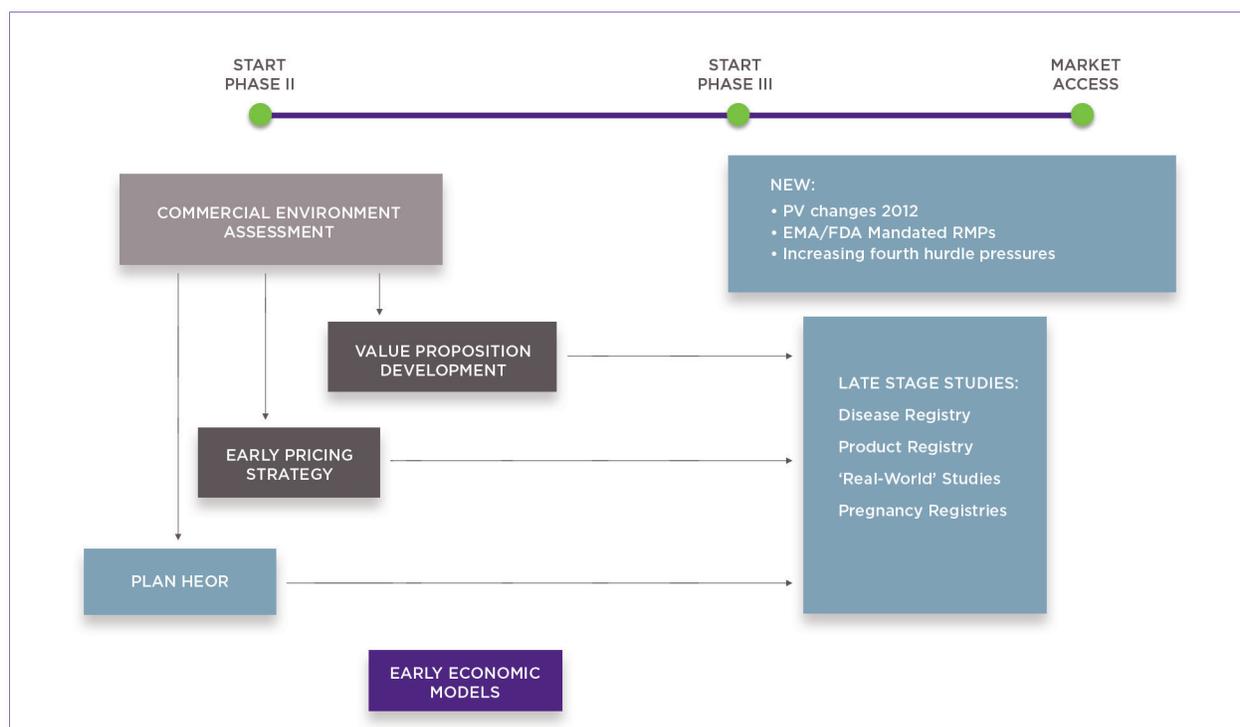


Diagram 2. Earlier Planning of Late Stage Studies as Part of the Clinical Development Plan.

This challenging new environment of post-regulatory requirements will require pharmaceutical companies to develop the Phase IV plans for IMP at a far earlier stage, and we suggest that should become a routine part of the clinical development program as illustrated in diagram 2. This will require a unique collaboration between the traditionally “siloes” research and development groups and medical affairs teams in pharmaceutical companies with those organizations carrying out their clinical trial program.

CONCLUSION

In this white paper we have explained the issues surrounding non-adherence in asthma studies, comparing clinical trials with real-world settings. Adherence in asthma studies needs to be measured and measured accurately to interpret outcomes in clinical trials.

As we look to the future we see a number of challenges in the short- to medium-term in this area. How can we create a more patient-centric model to address these issues? How can we use social media to help with adherence, whilst avoiding the known pitfalls such as under-reporting of adverse events and the perception of advertising of products in a non-compliant manner? And finally, in the era of “big data” how can we utilize the large data sets available to create prospective cohorts to monitor adherence rates on specific products? In addition to the considerations stated in this paper, the questions above will need to be further explored in order to appropriately address compliance issues in asthma clinical trials.

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Professor Liam Heaney, a world leading expert in adherence issues in asthma studies, brings 24 years of clinical research experience focused in difficult to manage asthma. Professor Heaney has developed a research program that spans the entire spectrum from clinical assessment and management to the development of novel biomarkers and translational therapeutics. He founded and now co-ordinates the British Thoracic Society UK Severe Asthma Network and National Registry on Difficult Asthma. The Registry facilitates research into the assessment and clinical management of difficult asthma and standardizes UK specialist clinical services.

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