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Optimising outcomes for adults with Cystic Fibrosis taking CFTR modulators by individualising care: Personalised data linkage to understand treatment optimisation (PLUTO), a novel clinical framework.

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Abstract:	Cystic Fibrosis (CF) is a life-limiting, inherited condition in which a novel class of oral medicine, CFTR modulators, has revolutionised symptoms and health indicators, providing an opportunity to evaluate traditional treatment regimens with the hope of reducing burden. Additionally, there is cautious optimism that life expectancy for people with CF born today could ultimately compare to that of the general population. Given this potential, there is a need and requirement to optimise treatment to balance burden with the best clinical outcomes for each person with CF in an individualised manner. Personalised data-Linkage to Understand Treatment Optimisation (PLUTO) is

	a clinical framework, developed within the 14-Centre UK CFHealthHub Learning Health System collaborative, designed for use at an individual level for people with CF taking CFTR modulators. The PLUTO framework encourages use of two routinely collected clinical outcome measure (FEV1and BMI) to determine health status. Where FEV1 or BMI trends suggest that optimal health outcomes are not being achieved for a person with CF, PLUTO supports consideration of adherence to both CFTR modulators and inhaled therapy to help guide the next steps. PLUTO is designed to support people with CF and their clinical teams to individualise care and optimise outcomes for those taking CFTR modulators, using data available in routine clinical encounters.
Response to Reviewers:	Please see attached "Response to Reviewer's" file.

Optimising outcomes for adults with Cystic Fibrosis taking CFTR modulators by individualising care: Personalised data linkage to understand treatment optimisation (PLUTO), a novel clinical framework.

INTRODUCTION

Cystic Fibrosis (CF) is a long-term condition resulting from an inherited genetic defect in the CF transmembrane conductance regulator (CFTR) gene (1). It affects approximately 162,000 people worldwide including 11,000 people in the UK, where current life expectancy of someone born today with CF is 56 years (2, 3). The leading cause of death is respiratory failure, resulting from recurrent lung infections and chronic inflammation (4).

Traditionally, treatment for CF lung disease targeted the downstream consequences of CFTR dysfunction in the respiratory tract, such as chronic infection and mucus hyperviscosity, through physical and inhaled (typically nebulised) therapy (5). Over the past decade, a novel class of oral medicine, CFTR modulators, have been developed, which restore or enhance function of the CFTR protein at the cellular level (6). There are currently four available CFTR modulators. Two of these, ivacaftor (Kalydeco®, Vertex Pharmaceuticals) monotherapy and elexacaftor/tezacaftor/ivacaftor (ETI, Kaftrio®, Vertex Pharmaceuticals) triple-therapy are considered "highly effective" given impressive improvements in lung function and body mass index (BMI) demonstrated in pivotal randomised controlled trials (RCTs) (7, 8). The advent of highly effective CFTR modulators provides an opportunity to re-assess the role of the traditional treatments with the intention of reducing treatment burden, which is a key priority for the CF community (9).

With the list price of CFTR modulators exceeding $250,000 per person per year, access is predominantly restricted to those in high income countries, covering less than 20% of the worldwide CF population (10, 11). ETI became available to people with CF in the UK through a commercial access agreement within the National Health Service (NHS) in August 2020. As ETI is a triple-therapy which also includes the active ingredient of ivacaftor monotherapy, it is the only commercially available highly effective triple molecule combination CFTR modulator. Approximately 90% of people with CF in the UK are eligible to receive ETI based on genotype eligibility criteria (12).

ETI has the potential to transform the long-term outlook for people with CF, with some hope that the life expectancy for people with CF could soon equate to that of the general population, at over 80 years (13). This potential is predicated upon a reduction in the rate of

long-term lung function decline, which is typically measured by forced expiratory volume in 1 second (FEV_1). In the pre-ETI era, the percentage of predicted FEV_1 typically declined at a rate of 2 percentage points (notation 2% used in this article) per year (14).

However, there is significant inter-individual variation in the magnitude of response to ETI. Approximately 10% of participants in the ETI RCT treatment arm experienced either no improvement or even a worsening in sweat chloride or FEV_1, whereas a further 10% experienced FEV1 improvements of over 30% (7). Recognising this, a framework was recently proposed which attempts to optimise outcomes in those who appear to demonstrate a low or absent response to ETI (15). This framework advises consideration of CFTR function biomarkers, such as rectal organoids and complex alleles to distinguish between partial or absent responses, though these measures are not routinely available in clinical practice.

ETI is the only commercially available triple molecule CFTR modulator, meaning that there is no alternative for someone who experiences a partial or low response. Therefore, if ETI treatment is already taken as prescribed but the clinical outcome is sub-optimal, then optimising the concurrent use of pre-existing treatments for CF, including inhaled therapy, may be the best therapeutic option. We propose a pragmatic approach which considers adherence to both ETI and inhaled therapies, alongside FEV_1 and body mass index (BMI) data, in determining how best to individualise care and optimise outcomes for adults with CF taking ETI.

THE PLUTO CLINICAL FRAMEWORK

Personalised data-Linkage to Understand Treatment Optimisation (PLUTO) was conceptualised in a single UK adult CF Centre and was then developed collaboratively with clinicians across the CFHealthHub Learning Health System. The CFHealthHub Learning Health System is a community of practice involving 14 UK adult CF centres. Adults with CF in these centres are offered nebuliser devices with electronic data capture capability, thus making real-time adherence data available to them and their clinicians through a cloud-based digital platform (16). Adherence data then facilitates a personalised behaviour change intervention which enables adults with CF to develop habits for treatment-taking (17). Whilst no change in

the primary endpoint of exacerbation frequency was identified, use of the CFHealthHub intervention and digital platform delivered sustained, significant improvements in adherence and habit, alongside a reduction in perceived treatment burden and rate of FEV_1 decline in a 52-week, 607-participant RCT (18). This demonstrated that CFHealthHub is an evidence-based approach to supporting adherence to inhaled therapy.

Adults with CF should receive regular specialised multi-disciplinary team (MDT) reviews to monitor health status and individualise their care (19). FEV_1 and BMI are routinely and widely collected in all CF consultations (19). Accelerated FEV_1 decline is associated with worse outcomes, including mortality (20, 21). BMI is a second key measure, with a falling or sub-normal BMI associated with worse outcomes (5, 22).

The PLUTO framework can be applied at an individual level among adults with CF taking CFTR modulators and recognises that not everyone requires identical treatment or a 'one size fits all' approach. PLUTO proposes using routinely collected FEV_1 and BMI as indicators of health status and then prompts consideration of adherence to CFTR modulators and inhaled therapy (and other pre-existing CF treatments) or suspicion of new pathology in those with sub-optimal health status (Figure 1).

Step 1: Assess FEV_1 and BMI status.

Step 1 considers six datapoints – pre-ETI FEV_1 and BMI, peak post-ETI FEV_1 and BMI, and current FEV_1 and BMI. In line with the assumptions of the model suggesting the potential for normal life expectancy (13), we propose a ≤1% annual decline in FEV_1 as a guide to determine satisfactory lung function. This is consistent with other modelling work conducted in adults with CF taking CFTR modulators, which highlighted the potential differences in life expectancy with small (1%) changes in rate of FEV_1 decline over time (23).

In consultations, determining whether an FEV_1 or BMI trend is satisfactory is complex, in part due to the natural variability of FEV_1 readings, requiring an individualised decision between the adult with CF and experienced CF clinicians. Determining whether lung health is satisfactory is also multi-faceted. For example, should someone on ETI have had FEV_1 stability

over 12 months at the cost of 70 days of inpatient intravenous antibiotics, their lung health might not be considered fully optimised. Alternative lung outcome measure, such as lung clearance index or imaging, are not routinely accessible but could be incorporated as part of an individualised assessment of lung health, if locally available. Functional outcomes, for example exercise testing, may also provide additional information and could be incorporated into the framework by local clinical teams.

A stable BMI of ≥23 for males and ≥22 for females, has historically been associated with optimal FEV_1 outcomes for adults with CF and is still the current CF Foundation recommended weight target (24, 25). Since the introduction of CFTR modulators, overweight and obesity are increasingly recognised but how these affect outcomes is still uncertain (26). The real-world ivacaftor data demonstrated that BMI continued to increase over the first 5 years of treatment (27). An unintentional fall in BMI should alert the clinical team to the possibility of reduced adherence to the CFTR modulator, prompting direct investigation of adherence and, where applicable, sweat chloride testing, as recently proposed for the investigation of inadequate CFTR modulator response (15). If there remains uncertainty as to whether the FEV_1 or BMI trend indicates optimal clinical status, especially with the natural variability of FEV_1 readings, clinicians may arrange early follow-up to ensure that emerging decline is identified more promptly.

Step 2: Determine adherence to CFTR modulator.

Routine electronic adherence data capture is currently unavailable for CFTR modulators. Patient self-report is the most widely used method of measuring adherence without electronic data capture, but the influence of social desirability bias and unreliable recall tends to result in over-estimation (28). Medicines possession ratio (MPR) is also used to estimate adherence and in the case of ETI, at least in the UK, it is possible to access delivery data from pharmacy companies (29). However, receiving deliveries does not guarantee that medicines are taken as prescribed (30). For the purposes of PLUTO, interruption of deliveries may suggest lower adherence, but in adults with no interruption in deliveries, who are experiencing weight loss or FEV_1 decline, tactful, sensitive clinical questioning needs to

explore the possibility of missed doses. Missed doses could be a particular problem for twice daily CFTR modulator regimens, such as ETI, where recommendations specify a minimum interval between doses. Clinicians may also explore factors known to impact CFTR modulator effectiveness, such as ensuring they are taken with fat-containing food and pancreatic enzyme replacement therapy (if indicated) and ensuring that doses are not being inappropriately combined.

It should be noted that therapeutic drug monitoring is not routinely available and therapeutic levels for ETI are not yet defined. Sweat chloride measurement may provide some insight into short-term adherence but does not necessarily provide insights into longer-term adherence, akin to using random glucose levels instead of continuous glucose monitoring to assess glycaemic control of people with diabetes. Perhaps unsurprisingly, there is a lack of association between changes in sweat chloride following initiation of CFTR modulators and longer-term health outcomes e.g. FEV_1 at an individual level (31, 32).

Step 3: Determine adherence to nebulised treatment regimen.

Whilst effective, inhaled treatment can be highly burdensome and average adherence to inhaled therapy regimens is approximately 40% (33-37). Higher adherence is associated with better clinical outcomes (38). Self-reported adherence to inhaled therapy is unreliable and the PLUTO approach advocates the use of objective adherence data from nebulisers with electronic data capture capability, as recommended in a recent Cochrane review (39, 40).

The CFHealthHub Learning Health System provides a cloud-based platform for capturing objective nebuliser adherence data. If electronic data capture devices are not available, then alternate methods such as patient self-report or MPR may be used, though these methods typically over-estimate adherence compared to electronic data capture. They are also unable to provide granular data to support the targeting of an adherence intervention or to determine, in real time, if adherence is improving with intervention (39).

Where adherence to inhaled therapy appears adequate, yet FEV_1 decline suggests suboptimal lung health, clinicians are prompted to consider the development of new pathology. This may

include, but is not limited to, a new diagnosis of CF-related diabetes, allergic bronchopulmonary aspergillus (ABPA), or infection with emerging lung pathogens such as *Mycobacterium abscessus*.

Of note, common CF pathogens, such as *Pseudomonas aeruginosa*, are characterised by an ability to persist despite treatment with antimicrobial therapy (41). Prolonged use may lead to antimicrobial resistance, necessitating periodic regimen reviews to maintain effectiveness. For example, if a person with CF was prescribed inhaled colomycin for the preceding 10 years, effectiveness may have waned. One way to assess this might be to alternate colomycin with another antibiotic and then compare the FEV_1 by treatment month, or to use other inhaled antibiotics such as aztreonam.

Scenario 1: FEV_1 and BMI satisfactory

Satisfactory FEV_1 and BMI indicate that the current treatment regimen and adherence are sufficient, instilling confidence in clinicians and individuals with CF. This potentially allows adults with CF to avoid being overburdened by treatment.

For example, if an adult with CF had reduced their treatment burden by discontinuing inhaled therapy, but annual FEV_1 decline was ≤1%, they could simply be monitored, ensuring they sustain a lower treatment burden, instead of being offered adherence support. How much treatment is enough will differ for each person. When nebuliser adherence is objectively measured within the PLUTO framework over time, it may be possible to determine a personalised estimate of how much treatment is enough to maintain stability and achieve an annual FEV_1 decline of ≤1%.

Scenario 2: FEV_1 satisfactory but BMI unsatisfactory

Satisfactory FEV_1 with declining BMI should prompt clinicians to assess for CF-related diabetes or suboptimal pancreatic enzyme adherence (42, 43). It seems less likely that weight loss would be related to CFTR modulator non-adherence if FEV_1 is stable, however each person should be considered holistically.

Scenario 3: FEV_1 unsatisfactory but BMI satisfactory.

Real-world ivacaftor data suggest that unsatisfactory FEV_1, despite a satisfactory BMI, is the most common scenario (27). The likely explanation is satisfactory CFTR modulator adherence but unsatisfactory use of other pre-existing treatments, for example low adherence to inhaled therapy. Pharmacy records confirming regular, uninterrupted CFTR modulator deliveries would also suggest that an exploration of adherence to other pre-existing treatments may be beneficial.

If adherence to inhaled therapy is low, then an appropriate next step may be to offer adherence support, for example using the CFHealthHub habit formation intervention (17, 18). If adherence to inhaled therapy is high, then optimisation of other pre-existing CF treatments, for example airway clearance techniques, should be considered, as well as exploring the possible development of new pathology (as discussed in Step 3).

Scenario 4: FEV_1 and BMI both unsatisfactory

This clinical picture suggests suboptimal adherence to CFTR modulators and/or inhaled therapy and/or the development of new pathology. If CFTR modulator adherence appears satisfactory, then the inhaled treatment regimen and adherence to it should be evaluated alongside a search for new pathology and consideration of adherence to digestive enzymes, as described in earlier sections. If inhaled therapy adherence is low, supporting this would be a “treatable target” and is recommended alongside an investigation into new complications. If adherence to both CFTR modulator and inhaled therapy regimens is unsatisfactory, it may be wise to initially focus on CFTR modulator adherence and consider inhaled therapy adherence support in due course.

ILLUSTRATIVE CASE

Following initiation of ETI, Alex, a 30-year-old person with CF, had a peak post-ETI FEV_1 of 95% and BMI of 23.1. At review, Alex’s FEV_1 is still 95% and BMI is 23.4, both of which are

considered to be satisfactory. No other clinical concerns are identified. Alex's ETI deliveries (assessed via pharmacy records) are regular, at the expected 3-monthly intervals, and Alex's nebuliser adherence (assessed via CFHealthHub) is 94%. As such, Alex's current treatment regimen and adherence to it may be considered satisfactory. Alex's treatment appears to be optimised, which would suggest they are on course to achieve an optimal clinical outcome (13). At this point, even if Alex was not using any inhaled therapy, there may be no immediate need to discuss any treatment changes. The PLUTO flow chart could be followed as per Figure 2.

One year later, Alex's FEV_1 is 90% (from 95%) and BMI is 23.5. (from 23.1). Alex's ETI adherence appears to remain high as does their nebuliser adherence at 98%. Although Alex appears to be using inhaled therapy as prescribed, their FEV_1 has dropped by 5% over the preceding year. This may alert clinicians to two possibilities. Firstly, the prescribed inhaled therapy regimen may no longer be adequate. Secondly, there may be the emergence of new pathology (Figure 3).

A further 6 months later, Alex's FEV_1 is 85%. BMI remains satisfactory, as does their ETI adherence, but their nebuliser adherence has fallen to 30%. The fall in nebuliser adherence may be contributing to the unsatisfactory FEV_1. Therefore, Alex may benefit from adherence support (Figure 4).

DISCUSSION

PLUTO is a clinical framework developed by an MDT of clinicians across 11 UK adult CF Centres, with the aim of individualising care for adults with CF and optimising outcomes. In the CFTR modulator era, PLUTO supports clinicians to pay attention to specific pieces of information (namely FEV_1, BMI and adherence), to structure clinical assessments and to guide next steps.

Whilst FEV_1 and BMI are routinely used in CF consultations and offer a useful starting point for assessing health status, CF is complex, and determining satisfactory lung health may extend beyond trends in these measures. PLUTO can be adapted to suit local needs and incorporate additional assessment tools, such as lung clearance index, if locally available.

After assessing an individual's health status, clinicians can then personalise their treatment recommendations to balance treatment burdens with the aspiration of optimising health outcomes. For example, someone not using inhaled therapy who has a stable FEV_1 may not require an adherence support intervention. PLUTO is in line with the 2024 UK CF Trust Standards of Care, which advocates the individualisation of care and shared decision-making, accounting for people's perspectives on balancing the benefits of treatment with treatment burden (19). Furthermore, by understanding the role of inhaled therapies at an individual level, there is the potential to reduce the environmental impact of medicines waste. The importance of this has been highlighted in the CF Trust Standards of Care and is in line with the World Health Organisation's determination that climate change presents a fundamental threat to human health (19, 44).

Optimisation of outcomes for adults with CF taking ETI is important because the availability of highly effective CFTR modulators does not necessarily guarantee excellent health outcomes for everyone. Ivacaftor, the first highly effective CFTR modulator did not quite deliver the expected results. An open-label study among previous trial participants showed a 47% reduction in FEV_1 decline three years post-Ivacaftor (45), yet real-world UK data demonstrated unabated FEV_1 decline such that FEV_1 returned to pre-ivacaftor levels within 5 years despite sustained weight improvements (27). Unless lessons from ivacaftor are learned and attention is being paid to optimise the health outcomes of adults taking ETI, there is a risk of squandering the potential long-term benefits.

Using a systematic framework like PLUTO to individualise care, with a view to optimising long-term outcomes, is a critical facet of long-term condition care. Asthma was recently revolutionised by the advent of monoclonal antibody therapy, referred to as 'biologics'. In contrast to CF, where ETI is considered the only highly effective modulator for most adults, there are multiple biologics available for adults with asthma, with different mechanisms of action that can be considered for those with an inadequate response. A pragmatic approach to choosing the correct biologic was recently published, recognising the importance of individualising treatment decisions to optimise long-term outcomes (46).

A challenge of optimising outcomes in long-term conditions is the need to consider long-term outcomes alongside short-term effects. For example, in people with atrial fibrillation (AF), oral anticoagulation reduces the long-term risk of stroke (47). People with AF who commence oral anticoagulation may derive no short-term benefit, and in fact, may experience side-effects. However, the rationale for this treatment is for the long-term, not short-term, benefit. In Rheumatoid Arthritis, another long-term condition, a "treat-to-target" approach improves long-term outcomes and supports treatment decisions (48). This involves frequently assessing disease activity, using a validated measure, and comparing it with a predetermined target. If the target has not been reached, then treatment is revised, and usually escalated, appropriately. By setting a target of achieving an annual decline in FEV1 of ≤1%, PLUTO also offers the potential for treat-to-target in CF. Over time, with more research, the pre-specified health status targets for the best outcomes in those taking ETI can be further defined in CF. PLUTO offers a starting point, which is consistent with the best available evidence (13).

A key strength of this work was collaboration between clinicians across 11 centres in the CFHealthHub Learning Health System, where these measures are influencing CF care. PLUTO is pragmatic and advocates the use of routinely collected measures (FEV_1 and BMI) and currently available treatment options, which provides the opportunity for implementation in any CF centre. PLUTO can also be adapted to incorporate novel measures or treatment options as they become available in the future. By using FEV_1 and BMI within PLUTO, adults with CF can be supported to make changes to their maintenance treatment regimens, allowing the opportunity for burden reduction whilst optimising their outcomes. The framework is flexible and can be adapted to local contexts. Indeed, we recognise the importance of local context when it comes to implementation. Local experience, resources, and epidemiology would mean some variation in the investigations and therapeutic strategies (e.g. use of sweat chloride testing) from site-to-site. PLUTO can also be adapted to incorporate novel measures or treatment options as they become available in the future. PLUTO offers the potential to understand, at an individual level, how much maintenance treatment is enough in the CFTR modulator era, whilst large population-based studies, such as NEEMO, CF STORM and SIMPLIFY are underway (49-51).

Qualitative work understanding clinicians' perspectives and the application of the PLUTO framework is ongoing, alongside an exploration of the views of adults with CF on treatment taking in the post-CFTR modulator era. The perspectives of both clinicians and adults with CF will be important in future refinements of the framework. Whilst it is inherent for clinicians to want the best outcomes for their patients, the perspectives of the people living with CF day-to-day must not be forgotten. A "satisfactory", or indeed "unsatisfactory", FEV_1, BMI or adherence level for clinicians may not mirror what is considered "satisfactory" or "unsatisfactory" to the person living with the condition. A single centre study suggests that adults with CF are willing to trade substantial reductions in FEV_1 to reduce treatment burden (52). However, it is crucial that both adults with CF and clinicians are fully informed of the potential implications of decision-making to reduce treatments on long-term outcomes. Intrinsic human cognitive biases, such as "present bias", can lead to decisions being made based on short-term rather than long-term considerations (53).

"*Good Medical Practice*", which sets out standards of care and behaviour for UK medical professionals, states the duties to "*Protect and promote the health of patients and the public.*" and "*Listen to patients and work in partnership with them, supporting them to make informed decisions about their care*"(54). A key skill for clinicians caring for individuals with long-term conditions to promote health is the ability to sensitively highlight the sacrifices involved in daily self-care by emphasising the long-term health benefits that today's efforts will yield in the future. Likewise, to ensure that the person with CF is not reduced to a series of numbers, as could be the case with any clinical framework, there is a need for clinicians to understand and acknowledge context and the complex range of factors that influence health outcomes and adherence, in line with the 2024 CF Standards of Care (19, 55).

A limitation of this framework is the inherent complexity in determining health stability. The natural variability of FEV_1 measurements makes aiming for tight FEV_1 margins problematic, so interpreting any single FEV_1 value involves paying attention to both trends over time, as well as the presence of respiratory symptoms (56-58). Applying a 1% threshold in assessing short-term changes in FEV_1 would be challenging, therefore clinicians may recommend that FEV_1 is measured more frequently, and in a consistent way, to reveal trends. In the short-term (i.e. visit-to-visit), the difference in clinical outcomes between a 1% and 3% decline in FEV_1 may

be minimal, but long-term modelling of life-expectancy suggests the cumulative effect may be substantial. For example, a 1% annual decline may give a life expectancy into the 80s, whereas a 2%, 3% and 4% decline may lead to a life expectancy closer to 60, 50 and 40 years, respectively (23). Now that ETI has been available for four years in the UK, it seems an appropriate time for clinicians to review lung function trends for adults with CF since starting ETI to consider how an individual's rate of decline may influence their life expectancy.

Another limitation is the accurate measurement of adherence. CFTR modulator adherence can be estimated through pharmacy delivery data but is mostly estimated through self-report, which is notoriously inaccurate (39). CF Centres with access to nebuliser devices with electronic data capture capability, such as those used within the CFHealthHub Learning Health System, benefit from real-time objective adherence data, but we recognise that other centres may be more reliant on delivery data or self-report, depending on local resources.

Lastly, it should be recognised that the intended application of PLUTO is for adults with CF who are treated with CFTR modulators. Approximately 10% of the UK CF population are not eligible for CFTR modulators and there are a proportion of people who discontinue CFTR modulators for reasons such as intolerance. Whilst we expect PLUTO to be applicable to the vast majority of adults with CF cared for at each CF Centre, this framework would require adaptation for those not prescribed CFTR modulators.

CONCLUSION

CFTR modulators present an exciting opportunity in CF, but since their introduction, there is uncertainty around the necessity of other long-established treatment regimens. PLUTO provides a systematic framework to help to manage that uncertainty at an individual level, and potentially balance the burdens and benefits of treatments. Using FEV_1, BMI and adherence data, treatment can be individualised, optimised and re-evaluated at sequential time points. PLUTO addresses uncertainties in applying population-level data to individuals, supporting tailored management plans to optimise outcomes and fully leverage CFTR modulators.

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FIGURE LEGENDS

Figure 1: The Personalised data-Linkage to Understand Treatment Optimisation (PLUTO) Clinical Framework. FEV1 = forced expiratory volume in one second. BMI = body mass index, CFTRm = Cystic fibrosis transmembrane conductance regulator modulator

Figure 2: Demonstration of how the PLUTO framework may support clinicians and a person with CF to determine if the current treatment regimen is adequate.

Figure 3: Demonstration of how the PLUTO framework may support clinicians and a person with CF to determine whether new pathology or a change in treatment regimen should be considered.

Figure 4: Demonstration of how the PLUTO framework may support clinicians and a person with CF to determine whether supporting adherence to inhaled therapy should be considered.

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Figure 1

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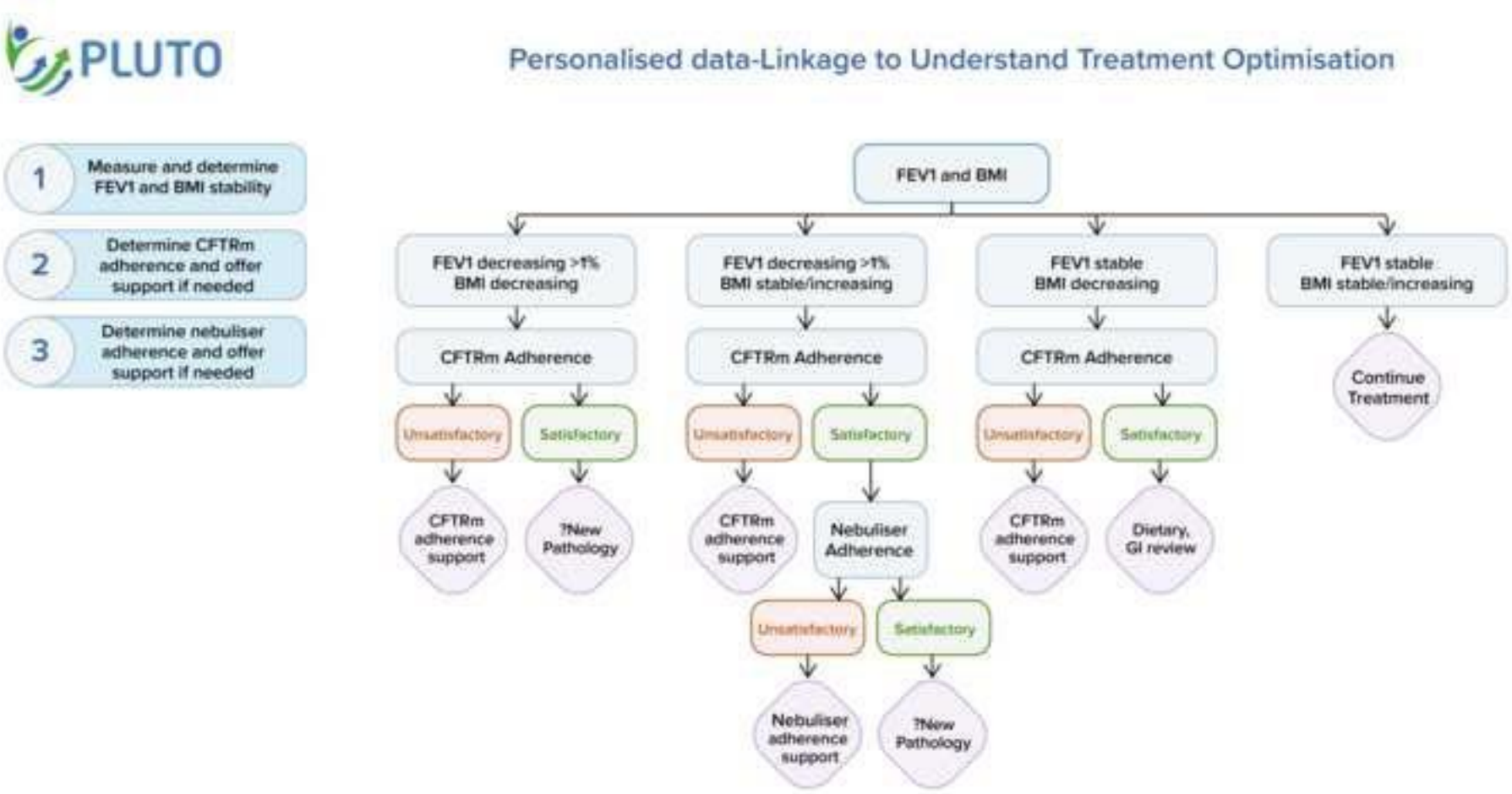

Figure 2

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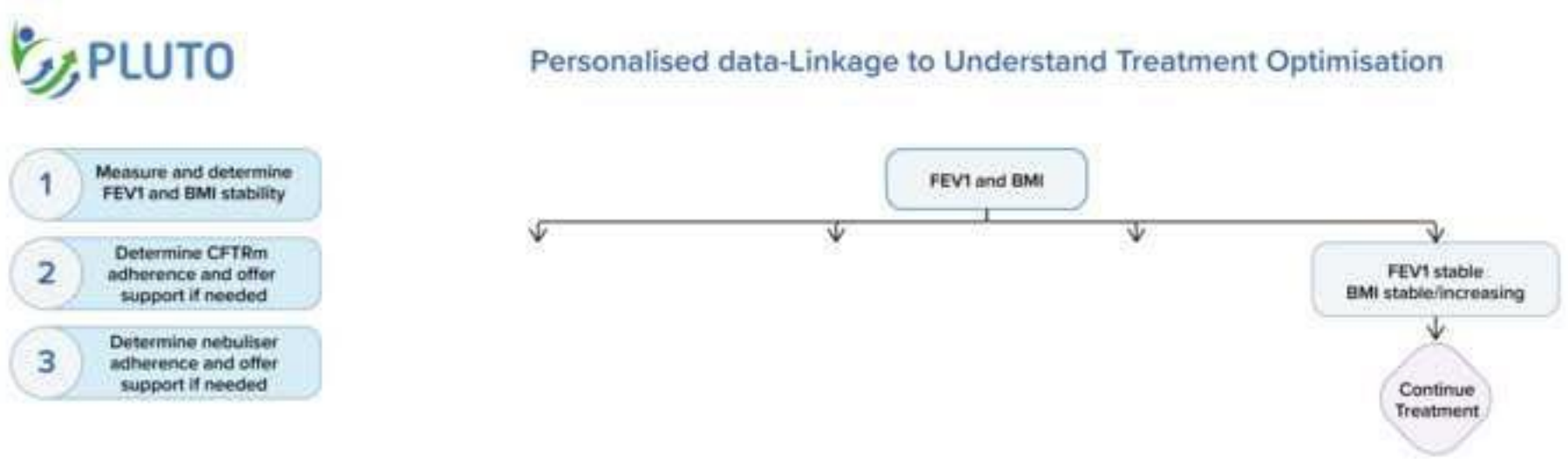

Figure 3

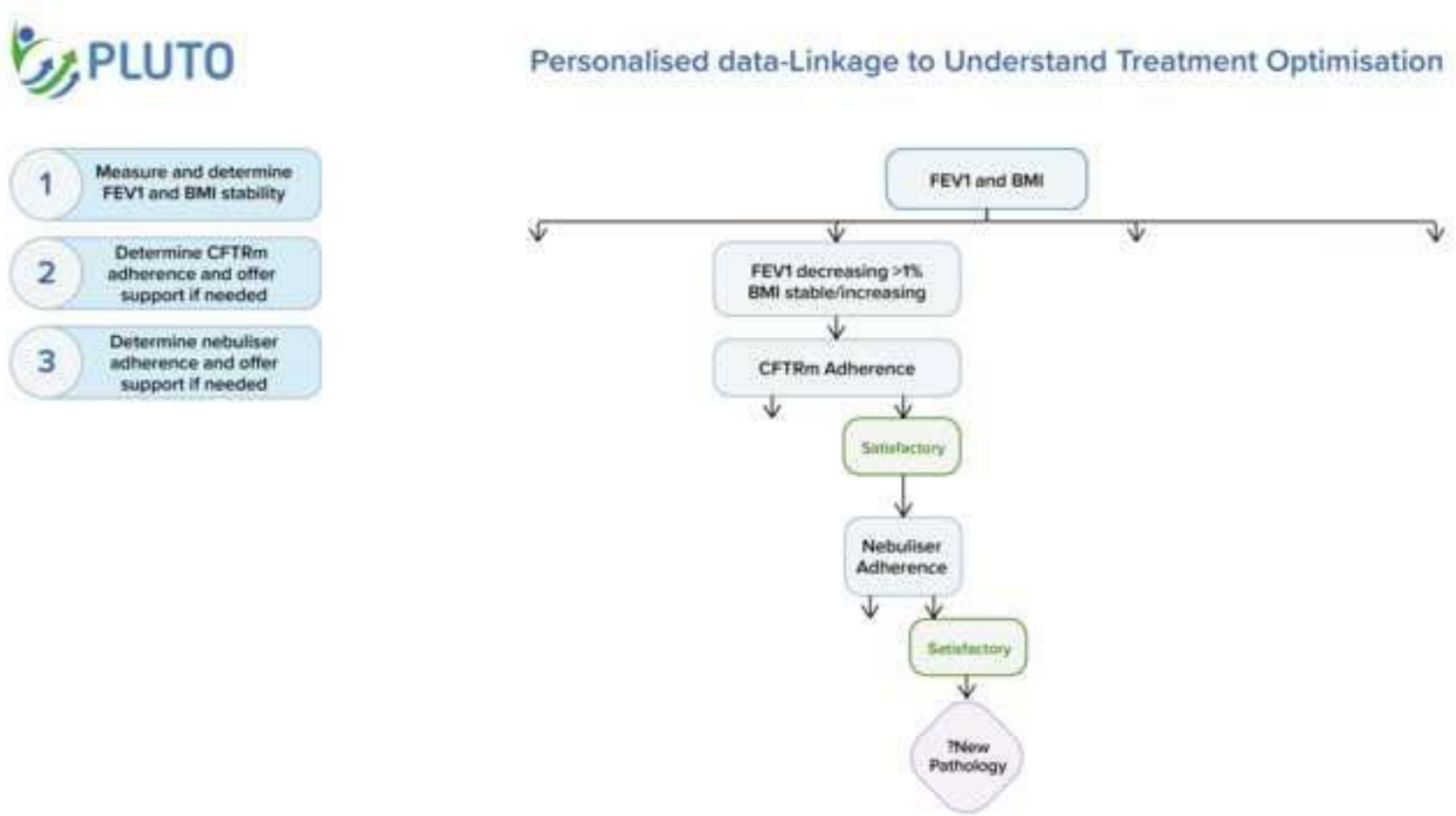

Figure 4