Table 4: Variations of Randomised Controlled Trials (RCTS) and alternative study designs

Study Design	Comments
Traditional randomised-controlled trials	RCTs are the most valid method for determining the efficacy/effectiveness of an intervention and reduce the potential for confounding bias, sample selection bias, information bias, and other forms of systematic bias. They allow both individual interventions (e.g. a specific technique for chest clearance) and packages of care (e.g. an exercise and education based rehabilitation programme) to be tested and allow estimates of both the absolute effect (against no treatment or placebo) and the relative effect (against alternative treatments) of an intervention to be assessed. They also allow comparison of, and correction for, imbalance in baseline characteristics between groups and comparison with a control or placebo group. The most commonly used RCT is the parallel-groups design.
Factorial RCTs	Factorial RCTs are useful when it is important to assess two or more interventions in combination. For example, comparing two treatments A vs B or A vs (A + B) or A vs B vs (A + B). They allow interactions to be identified and tested (i.e. when the effectiveness of one treatment differs according to the presence or absence of the other treatment). When no interaction exists, main effects are analysed (the effect of one treatment irrespective of the presence or absence of the other), whereas when an interaction is present it is important to analyse simple effects (the effect of one treatment separately for the presence and the absence of the other).
Cross-over trials	Cross-over trials are useful when within-patient comparisons seem more robust than between-patient comparisons. The effect of the treatments tested should be reversible. Attrition may be problematic in cross-over trials especially in CF.

Cluster randomised trials	Cluster randomised trials are useful when interventions are delivered to groups of patients rather than individual patients or when the intervention is delivered at the level of the practitioner rather than that of the patient. The required sample size is normally inflated with respect to an individually-randomised trial, and special methods of analysis are required that take account of the clustering of observations.
Equivalence trials	Equivalence trials are useful when the hypothesis is not to demonstrate that a new treatment is superior to the standard care, but that it is equally effective. A variant is the non-inferiority trial, where the concern is to show that one treatment is no less effective than another.
Preference trials	In an RCT, patients will be randomised to the treatment groups with no consideration given to their preferences. However, they may have a preference either for the standard treatment or for the new treatment, or may be indifferent. Those who receive their preferred treatment might be better motivated and comply better with the treatment programmes and report better outcomes. In a preference trial of two treatments A and B there could be four groups: randomised to A, chose A, randomised to B, chose B.
Fractional design	Fractional design use a reduced number of experimental conditions in a systematic way so that it allows the researcher to estimate main effects while higher interaction effects are no longer estimable.
Non-randomised controlled trials	Non-randomised controlled trials can be used in the following situations: treatment groups are pre-determined and cannot therefore be formed by randomization, e.g. treatment intervention in one group (e.g. hospitalized) and controls from another group (e.g. outpatients); randomization is unethical or inappropriate e.g. exposure to cigarette smoking. However it is important to check for selection bias e.g. baseline differences between the two groups (treatment group could have more severe risk factors, which may act as a confounder).
Cohort or case-	Cohort or case-control studies can seldom find two groups of subjects (exposure versus non-exposure in a cohort

control studies	study or cases versus controls in a case-control study) that are similar in demographics and risk factors, though some comparability can be achieved through matching. Controlling for baseline or follow-up differences in subject characteristics is primarily done during the statistical analysis stage; however not all possible confounders may have been considered. These designs are well suited for epidemiological studies, but harder to employ to answer questions of treatment effectiveness.
Cross-sectional surveys	Cross-sectional surveys (using postal questionnaires or more specialised techniques such as the Delphi) are helpful for descriptive research questions (e.g. what is current practice in the management of adult CF among specialist respiratory physiotherapists?; what are the attitudes and beliefs of younger patients with CF regarding dietary regulation?). Whilst useful for descriptions of practice, they have little role in the testing of practice. Surveys may also be used to determine prevalence or incidence rates with regard to a particular condition. Representativeness is especially important; subjects should ideally be randomly selected and not be volunteers.
Single-system (n=1) studies	Single-system (n=1) studies allow detailed evaluation of responses to intervention in a single patient (providing the intervention does not have an irreversible effect), and can control for a number of threats to internal validity. Extrapolating conclusions of treatment effectiveness from the individual patient to a broader population of patients may be difficult.
Case reports/series	Case reports/series can provide additional detail on modes of clinical practice and responses to treatment, but do not provide clear cause-effect conclusions on the relationship between intervention and outcome. These may provide hypotheses that can be tested in other designs, such as an RCT.
Secondary analysis	Examples of secondary analysis include registries, systematic reviews, meta-analysis (for quantitative studies) and meta-synthesis (for qualitative studies).

Qualitative designs	Examples of qualitative designs are focus groups, interviews (semi-structured, in-depth, narrative), and certain types of observation. These studies normally seek to answer exploratory research questions, and do not seek to address treatment efficacy/effectiveness or other cause-effect relationships.