Pragmatic Trials

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Pragmatism in clinical trials arose from concerns that many trials did not adequately inform practice because they were optimized to determine *efficacy* [1]. Since such trials were performed in relatively small sample sizes in expert sites with highly selected participants they could be overestimating benefits and underestimating harm. This led to the belief that more *pragmatic* trials were required, designed to show the intervention real world *effectiveness* in broad patient groups. Medical researchers, academic and commercial, must deliver healthcare innovations (drugs, devices or other interventions) that are safe, beneficial, and identify subgroups with greatest benefit relative to risk and are cost-effective. A broad view of an intervention, including approaches to improve its effectiveness, is critical. An ideal trial includes a population relevant for the intervention, a control group treated with an acceptable standard of care, outcomes that are meaningful, and conducted and analyzed to a high quality. Pragmatic trials frequently include complex interventions, sometimes consisting of several interacting components [2], often involving the skills and experience of one or more healthcare professionals to deliver the intervention – for example surgery, physiotherapy or cognitive behavioural therapy.

This article does not provide a definitive exposition of methodology for pragmatic studies, but rather we explore the contexts where a pragmatic design is most and least attractive, identifying the strengths and limitations of, and challenges in implementing, pragmatic trials.

What is a Pragmatic Trial?

Schwartz and Lellouch [1] proposed a distinction between explanatory trials confirming a physiological or clinical hypothesis and pragmatic trials informing a clinical or policy decision by providing evidence for the intervention's adoption into real world clinical practice. The original PRECIS tool [3] attempted to clarify the concept of Pragmatism and provided a guide, scoring system and graphical representation of a trial's pragmatic features. Features covered i) recruitment of investigators and participants, ii) the intervention and its delivery, iii) study follow-up and iv) study outcomes, their determination and analysis. Many trials could be deemed pragmatic on at least one

of these dimensions, but few are truly pragmatic on all. Pragmatism has been discussed widely [4-20], and a special issue of Clinical Trials had twelve articles focused on ethical and regulatory issues in pragmatic trials [e.g. 21]. The requirements for pragmatism were loosened significantly in PRECIS-2 [22] and a pragmatic extension to the CONSORT statement has been proposed [23]. Key dimensions for assessing the degree of trial pragmatism, following PRECIS-2, are given in Table 1. Trials used as pragmatic exemplars throughout this article are summarized in Table 2.

What are the greatest challenges to Pragmatism and potential solutions?

Recruitment of study participants (Dimensions 1, 2: Table 1)

Pragmatic trials require that trial participants are similar to those who would receive the intervention if it became usual care, which may be unknown for novel interventions. Participation in trials has fallen over time; for example, in individuals without established disease a less than 10% response to a screening invitation is common. The healthy volunteer effect and competing recruitment from other studies, particularly in academic centers, undermine attempts to achieve generalizability. Financial incentives associated with recruitment to industry studies can significantly impact recruitment to less well funded academic trials. Minimization of inclusion/exclusion criteria and reduction of the number and complexity of study visits, study procedures and questionnaire burden are important but likely only partial solutions to increased trials participation. In this regard, the development of large simple trials (e.g. Heart Protection Study [24] and CRASH [25]) has been important. The Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE) trial [26], a trial of thrombus aspiration before PCI versus usual best care prior to PCI involved 7244 participants and had a primary endpoint of 30-day all-cause mortality. The trial used a national registry (Swedish Coronary Angiography and Angioplasty Registry (SCAAR)), achieving high participation due to simple design and no need for additional study follow-up. The trial did not show a differential response to the treatments.

Informed consent is a barrier to unselected participant recruitment. To guarantee everyone eligible is included, this requirement would need to be waived. In some contexts it is possible, subject to ethical approval, to conduct trials without or with modified consent. The Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) cluster based trial [27] of usual versus full prescription coverage randomized 2980 healthcare plan sponsors, with a primary endpoint of first major vascular event or revascularization. In this study, which required consent from plan sponsors but not from patients, the elimination of copayments for drugs prescribed after myocardial infarction did not significantly reduce rate of the trial's primary outcome. A trial of emergency short term use of antiseptic versus antibiotic-coated versus plain latex catheters, to investigate the impact on the primary outcome of the incidence of symptomatic urinary tract infection for which an antibiotic was prescribed within 6 weeks, was analyzed in 6394 participants. [28] It randomized participants with retrospective consent after the initial admission. Routine use of antimicrobial-impregnated or antiseptic-coated catheters was not supported by the results of this trial.

If a trial neither interferes with normal clinical care nor adds non-standard activities or data collection, the objection to waiving consent is reduced. In low risk contexts, randomization of patients to alternative established treatments may be possible without consent [19], as might a cluster design to randomize physicians to prescribe only one of the alternative treatments. CRASH randomised >10,000 patients with head injury and impaired consciousness to determine if glucocorticoids, compared to placebo, impacted death and neurological disability. It was stopped early due to evidence that glucocorticoid treatment increased mortality [25]. In CRASH the nature of consent depended on local ethics decisions, with the need for consent being waived in many cases.

Cluster randomization as in MI FREE [27], involving groups of individuals (in the same healthcare facility) randomized to the same intervention, is popular in pragmatic trials. Cluster-cluster trials randomize clusters with outcomes aggregated at the cluster level, while cluster-individual trials have individual level outcomes. Cluster-cluster trials offer greater possibilities of waiver of cluster

member level consent [21, 29]. Cluster-individual trials offer the option of waiver of consent for the intervention with consent for participant follow-up. This approach was implemented in ASSIST, a cluster-randomized trial of a high school smoking prevention intervention with a primary outcome of smoking in the past week [30]. The trial suggested that the ASSIST intervention could lead to a reduction in adolescent smoking prevalence of public-health importance.

The ongoing High-STEACS trial [31] is investigating the clinical implications of a high sensitivity troponin-I biomarker for diagnosis of myocardial infarction with a primary outcome of cardiovascular death or recurrent myocardial infarction within 12 months of admission. Like MI FREE, this is a trial of policy change. It uses a stepped-wedge cluster design [32] where all sites transition from control to active intervention, but with randomization allocating the timing of transition with some sites allocating patients before others. Such trials of a policy which is going to be implemented anyway arguably offer the greatest potential for pragmatic studies with no individual consent while allowing for some degree of control of ecological changes in care that may be happening simultaneously.

To summarize, pragmatic trials face some unique and many of the same challenges that are seen with traditional explanatory trials. Strategies to enhance recruitment have been proposed [33]. Where appropriate, various forms of cluster randomization offer advantages and may help avoid informed consent. Disease registries provide patient cohorts consented for registry inclusion, facilitating recruitment and follow-up. A related approach is the cohort multiple randomized design [34], within which a cohort of participants is recruited and consented for follow-up and possible recruitment into trials of new treatments versus standard care. In any particular trial, only participants randomized to the novel intervention are further consented, reducing the concerns of participants randomized to usual care.

Recruitment of investigators (Dimension 3: Table 1)

Trials need investigators to take responsibility for recruitment, treatment and follow-up. Many health care professionals outside academic centers do not participate in clinical trials, in part because of the time pressures associated with delivery of their clinical duties and for some because they do not consider research to be a key component of their job. Hence, study investigators will often not provide the heterogeneity of practice present in usual care. In contrast, in the TASTE trial [26], investigators across Sweden contributing to a national quality registry were included. Good studies include a variety of investigators with a representative mix of experience appropriate to the intervention studied. The trial of short term use of antiseptic versus antibiotic-coated versus plain latex catheters [28] made significant efforts to include a heterogeneous group of hospitals, specialists and surgical procedures. Despite these examples, this is a dimension where many studies fail the pragmatism test. A pragmatic approach is easier where an intervention is implemented at a group rather than an individual level, one reason why pragmatic trials are commonly cluster randomized. In the ASSIST trial only 113 (48%) of 233 possible schools expressed an interest to participate in the study [26]. The percentage of potential clusters agreeing to take part will vary depending on the trial context. A trial run by an overarching authority may achieve much higher participation. For example, a hospital could insist on full involvement of all wards in a trial of approaches to infection control.

The wrong type of heterogeneity can be harmful. For example, a study of community heart failure nurses in reducing emergency heart failure admissions, incorporating many countries with poorly developed health care systems, would not inform implementation in a developed healthcare system. Likewise if an intervention involves significant technical expertise, then that intervention should be delivered by individuals with an adequate throughput of patients to enable them to maintain their levels of expertise. This is particularly true in surgical trials where complex surgery is increasingly delivered in high throughput centers. This creates a conflict in designing pragmatic trials. Should we

conduct a study in the healthcare environment that currently exists, or in a context representing the current direction of travel in the relevant specialist area?

If heterogeneity of response to the intervention is likely, a study must be large enough to permit an understanding of that heterogeneity; this may require a substantial increase in sample size to detect a treatment by sub-group interaction. Often, there will be power to detect treatment by sub-group interactions only in large individual patient level meta-analyses.

Establishing a critical mass for the efficient trial conduct is crucial. Incentivizing investigators is important in the face of increasing demand to deliver clinical services more efficiently since research takes time over standard clinical care. The development of clinical networks and establishment of disease specific research communities is one way forward. Another would be to give credit to health professionals for research as a key component of professional work plans. In the United Kingdom these approaches along with the creation of a national network of registered as fit-for-purpose Clinical Trials Units has improved the recruitment and retention of clinical investigators and methodologists working together to deliver trials, avoiding the common approach of setting up a network to deliver a single trial that is then not reused for future studies [35].

The intervention and its delivery within the trial (Dimensions 4,5 and 6: Table 1)

A trial with blinded interventions is not fully pragmatic. In pragmatic trials the randomized group is commonly not masked. Efforts made to minimize biases in open trials include focusing outcomes on major events such as mortality and emergency hospital admissions as in Prospective Randomised Open Blinded Endpoint (PROBE) trials [36] such as the ASCOT-BPLA [37] and SPRINT [38] trials of the impact on cardiovascular events of different strategies for lowering blood pressure. However, the reporting of non-serious adverse events, reasons for treatment discontinuation and many patient reported outcomes, are subject to greater degrees of bias in open studies, impacting study quality. In the Initial Antidepressant Choice in Primary Care trial [39] of fluoxetine versus tricyclic drugs, a

policy trial of newer vs. older drugs as first line therapy for depression to study the consequences of initial antidepressant choice under usual care conditions, adverse events were a main study outcome. The open nature of the study could have compromised the integrity of this endpoint. In the trial, clinical and quality-of-life outcomes, and overall treatment costs provided no clear guidance on initial selection of fluoxetine or tricyclic drugs. The CRASH trial involved placebo control and blinding. Nonetheless, it had many pragmatic elements. In many situations the need to avoid reporting bias will override purist pragmatic considerations making blinding the optimal approach. In complex intervention trials where blinding the intervention is often impossible it is usually possible to blind the assessment of outcomes [36]. In any trial the advantages and disadvantages of blinding must be considered; blinding being particularly important where reporting of key endpoints or safety events could be biased in an open study.

In pragmatic designs the intervention should be delivered as in normal practice, by staff with typical experience using routinely available equipment. The MI FREE trial [27] tested a treatment policy assessing drugs within a class with flexible doses (a pragmatic trial often investigates a technology, not specific approaches within that technology). The degree of support for participants in treatment persistence can influence outcome. Traditional trials have study visits involving discussion of compliance and recording of safety laboratory tests and other investigations beyond normal practice. A trial dominated by poor delivery of the protocol or intervention is of limited use. Ideally a balance should be achieved, taking into consideration both the intervention and its mode of delivery. Investigators should be given basic advice on how to achieve good outcomes for participants, and reasonable levels of training in novel interventions within the constraints of the environment within which the trial is conducted.

The nature of study follow-up (Dimension 7 Table 1)

Collecting trial outcomes unobtrusively is attractive, reducing participant and investigator burden without introducing artificial aspects to follow-up. This is most feasible in healthcare systems with

reliable and accessible electronic health records capturing the events of interest. This might be achievable where there is a unified electronic healthcare record, but is at present challenging in many countries. The High-STEACS trial [31] illustrates the potential of this approach, with no study-specific data collection visits at all. Likewise, MI FREE [27] followed participants via a healthcare database with outcomes determined algorithmically. Record linkage to routinely collected health records in the West of Scotland Coronary Prevention Study (WOSCOPS) [40-43] illustrates the benefits in identifying serious adverse events and potentially replacing traditional within-trial endpoint determination, and in evaluating long-term post-study safety, efficacy and cost effectiveness. An attractive alternative to electronic health record trials are trials of alternative interventions in patients already enrolled in disease or intervention specific registries that incorporate a detailed patient phenotype and long-term follow-up. This provides an efficient and low-cost opportunity for the conduct of pragmatic studies (e.g. TASTE [26]).

The nature of study outcomes, their determination and analysis (Dimensions 8, 9 Table 1)

Pragmatic endpoints should be important to patients, for example major life events (e.g. death, or emergency hospital admissions). Pragmatic trials are also often large, identifying modest treatment effects and assessing safety in unselected populations for under-investigated interventions. They are also often simple, minimizing study procedures and data collection requirements. The CRASH trial [29] achieved a high degree of simplicity with a 2-page case report form. The catheter study [28] had a primary outcome of symptomatic catheter associated UTI up to 6 weeks post hospital discharge, rather than lab-confirmed infections in hospital, emphasizing the importance of health resource usage over mechanistic outcomes.

Symptoms, disability and quality of life are commonly key outcomes in pragmatic trials. Unlike major life events, signs and symptoms and quality of life measures are seldom recorded consistently in routine practice requiring patient visits or completion of questionnaires. Pragmatic trials often use mailed questionnaires or web-based forms to avoid study visits. This reduces cost but can incur

substantial missing data with challenges for analysis and interpretation. Offering participants alternative methods of providing responses, including mobile phones and other handheld devices might increase response rates. Research into shorter effective Patient Reported Outcome questionnaires continues [43]. The ASSIST trial [26] achieved a > 90% return of self-reported data, an unusually high level. In mental health and other areas where many outcomes are questionnaire based, direct follow-up is difficult to avoid. For example, the Initial Antidepressant Choice in Primary Care trial, [37] (a study with an otherwise pragmatic design), had study visits at 1, 3, 6, 9, 12, 18, and 24 months after randomization. The main results of the trial were based on the first three study visits and 91% of these visits were completed. Quality of life outcomes play an important role in cost-effectiveness analyses, a common feature of pragmatic trials as illustrated in MI FREE [27] and the Initial Antidepressant Choice in Primary Care trial of fluoxetine versus tricyclic drugs study [37]. Clearly, quality of life outcomes cannot be collected in a no-consent study such as MI FREE or in studies with follow-up within a registry or electronic health system such as High-STEACS [31] and TASTE [26], unless routinely recorded.

Pragmatic trials can provide long-term safety data in unselected populations. However, there are challenges in interpreting safety data which is often self-reported, or is subject to delays in availability, incompleteness, and coding variability associated with national registries. Explanatory trials can also present adverse event related interpretational challenges, as events are sometimes not collected after withdrawal from randomized treatment, introducing bias into statistical analyses.

It has been argued that pragmatic outcomes should not need adjudication. We believe this is a quality, rather than a pragmatic issue. If the quality and consistency of outcome ascertainment can be improved by adjudication without impacting normal patient care then surely that is desirable.

Discussion

Drug development involves cautious introduction of a novel substance into human subjects with gradual evaluation in patients with the relevant disease, to evaluate safety, early evidence of efficacy and appropriate doses for future evaluation. The development of non-drug interventions should, but often do not, involve proof of concept or pilot studies to tailor the intervention and evaluate its acceptability. Many such interventions also require selection of a dose, such as duration and intensity of physiotherapy or physical training. These trials by their nature could be, but need not be, pragmatic as they involve careful refinement of the intervention and assessment of potential value in clinical practice.

It is only after Phase III drug trials that we have any real understanding of whether the treatment is beneficial, who might benefit most, potential adverse effects and where the technology might be most cost-effectively implemented. The ideal time to carry out a pragmatic trial would be in the implementation stage of a complex intervention or the post-marketing phase of a drug, to help us understand what the impact of introducing the new technology might be on overall public health. This raises the question of who should pay for these studies. For drugs and devices, industry might feel that they have already done their bit getting a drug to the registration stage. Perhaps the best solution would be joint industry/ governmental funding.

Some studies by their context, and the intervention studied, are more pragmatic than others. Studies where the intervention is low cost, with few risks to participants and/or is applied at a cluster level, will almost automatically be more pragmatic in nature or easier to organize in a pragmatic fashion than studies with high cost complex interventions. Healthcare systems with comprehensive electronic records or with condition-specific registries offer excellent environments for pragmatic low-cost studies.

The conflict between mechanistic and pragmatic trials is often expressed as ‘greater internal validity of mechanistic studies’ compared with ‘improved external validity of pragmatic trials’. Price et al [45]

describe two pragmatic trials to evaluate the real-world effectiveness of a leukotriene-receptor antagonist (LTRA) compared with either an inhaled glucocorticoid for first-line asthma-controller therapy or a long-acting beta2-agonist (LABA) as add-on therapy in patients already receiving inhaled glucocorticoid therapy. Study results at two months suggested that LTRA was equivalent to an inhaled glucocorticoid as first-line controller therapy and to LABA as add-on therapy for diverse primary care patients. Equivalence was not established at two years. Non-adherence to the prescribed regimen was a major limitation. To mimic real-world practice, the investigators constructed two treatment strategies that rapidly developed considerable similarity. This undercut study power to detect differences in effectiveness of the drugs under investigation. They noted that 'the very features of pragmatic trials that support the generalizability, or applicability, of their results to real-world practice may also reduce assay sensitivity and therefore limit the interpretation of results'. These features include heterogeneous patient populations some of whom may not have the condition of interest, a lack of blinding, absence of a placebo group, and sub- optimal therapy adherence.

The integration of research and clinical practice by the development of ''learning healthcare systems'' advocated by the Institute of Medicine [46], with relevant clinical and patient reported outcome data collected by default, would create a natural environment for clinical research, although some have questioned whether this is feasible given the clinical delivery pressures within today's healthcare systems. [47, 48]

Pragmatism should not be synonymous with a laissez faire approach to trial conduct. The aim is to inform clinical practice and that can only be achieved by high quality trials. We believe that the concepts of internal and external validity and even the dichotomy between explanatory and pragmatic trials are overly simplistic. A better approach is to assess how a trial design adequately addresses the study's main objectives including its ability to inform clinical practice.

Conclusion

Some trials need not be forced to be pragmatic and others will naturally have pragmatic features because of the nature of the intervention and the healthcare context they are conducted in. Very few trials can be fully pragmatic. Studies of truly novel interventions can be game changers without being particularly pragmatic. No single trial, pragmatic or otherwise, is likely to answer all potential questions about the value of any healthcare technology. A pragmatic approach to pragmatism would be to adopt pragmatic trial features wherever feasible and sensible and where this does not compromise study quality and the ability to answer the clinical question of interest.

Disclosure:

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Table 1: The nine dimensions for assessing the level of pragmatism in a trial, as proposed inPRECIS-2 [grouped into four higher level domains].

Recruitment of investigators and participants
1. Eligibility—To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? 2. Recruitment—How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients? 3. Setting—How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial 4. Organisation—How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care? 5. Flexibility (delivery)—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care? 6. Flexibility (adherence)—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of study follow-up 7. Follow-up—How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
The nature of study outcomes their determination and analysis 8. Primary outcome—To what extent is the trial's primary outcome directly relevant to participants? 9. Primary analysis—To what extent are all data included in the analysis of the primary outcome?

Table 2: Exemplar trials and their main pragmatic features – highlighting the important design features that make these trials pragmatic

Trial	**Recruitment of investigators and participants**	**The intervention and its delivery**	**Study follow-up**	**study outcomes, their determination and analysis**
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE)	Registry Based RCT. Participants randomised within an existing registry for coronary angiography and angioplasty. High level of participation (~60% of eligible participants). Individual consent for the trial. Initial oral consent confirmed in writing within 24 hours.	The intervention was thrombus aspiration before PCI or usual best care prior to PCI.	No study follow-up visits. No study specific validation of national registry procedures or outcomes. Sample size increased due to low event rate.	Study data and outcomes extracted from registry database and record linkage to a national discharge registry. Safety – meta-analysis suggested increased risk of stroke. No loss to follow up.
Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE)	Cluster design, no individual participant consent. Controlled policy study ("value-based insurance design" or "evidence- based plan design"). Excluded those whose medications already fully covered.	Insurance plan sponsors randomised to usual or full prescription coverage. No special clinical interventions, all drugs within a class considered Study administered by commercial insurer.	Participants followed up remotely. Study follow up changed from a minimum of 1 year to minimum of 3 months.	Study outcomes determined algorithmically from healthcare databases. Economic evaluation. No patient reported outcomes (consistent with no consent) or safety reporting (increased compliance could mean higher side effects).
Antimicrobial catheters for reduction of symptomatic urinary tract infection (UTI) in adults requiring short-term catheterisation in hospital	Individually randomized trial of 3 catheter types in elective and emergency contexts. Retrospective consent for emergency cases. Heterogeneity of hospitals, specialties and surgical procedures.	Open design, active control, Impractical to blind catheters. 50% of emergencies did not confirm consent. 4% did not get a catheter, and another 4% did not get the catheter they were allocated to.	Primary outcome symptomatic catheter associated UTI. Secondary outcome confirmed catheter-associated UTI. Hospital and community based follow up (6 weeks post catheter removal).	No differences found, in contrast to the meta-analysis of generally small, single centre explanatory RCT – publication bias, highly select populations, lab-based outcomes.
Intravenous corticosteroid in adults with head injury (CRASH)	Individually randomised, placebo controlled	No consent (emergency surgery) – with local variations. Fixed dose of steroid to simplify, any patient eligible if treating doctor uncertain	Very simple: pragmatic outcome – all cause mortality; two page case report form; no record of concomitant medications or procedures.	Randomised around 10,000 in 239 hospitals in 49 countries. Follow up >99%, adherence 98%, 99% received the full dose. Study terminated early due to excess deaths on steroids.

		about giving steroids.		Immediate impact on practice.
An informal school-based peer-led intervention for smoking prevention in adolescence (ASSIST)	Cluster public health RCT of 59 schools (10730 pupils) 127/233 schools expressed an interest. 66 randomly selected from 113 agreeing. Individual consent for follow-up in a vulnerable group.	Complex intervention – smoking advice delivered by consensus identified class 'leaders'. Randomised at school level, outcomes aggregated at school level (year group).	Saliva samples for cotinine measurement	Analysis complicated – 'three tier hierarchical repeated measures model' High response rates (>90%). Low proportion withdrawn by parents (at start) or refused to participate (<5%).
High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS)	Stepped Wedge diagnostic policy study. Hospitals randomised to use standard Tropinin I assay or high sensitive Troponin I assay for the diagnosis of myocardial infarction. No individual consent for trial.	The new assay introduced into normal care pathways. Hospitals used older assay for all chest pain admissions until their randomised switch time after which the new assay was used for all chest pain admissions.	No study specific visits. Main outcome 1 year cardiovascular death or recurrent myocardial infarction. Consent required for samples for explanatory lab-based sub-study.	Study outcomes determined by linkage to national electronic databases of hospital discharge summaries, deaths, and other medical records. Outcome to be analysed using a 'Safe Harbour' approach.
Effectiveness and Cost of Fluoxetine vs Tricyclic Antidepressants (Initial Antidepressant Choice in Primary Care)	Head-to-head 'policy' RCT of newer vs. older drugs as first line therapy for depression to study the consequences of initial antidepressant choice under usual care conditions.	Open study to preserve usual care approach. Comorbidity or severity of depression not exclusions. 6% ineligible, 7% refused. No restriction on doses of study or concomitant drugs.	Follow-up assessments at 1, 3, 6, 9, 12, 18, and 24 months after randomization. Interviewers blinded to study intervention.	Multiple outcomes: clinical and cost effectiveness; adverse effects; quality of life. No restrictions on crossovers /discontinuations. May not be generalizable to different healthcare systems.
Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy	Primary care, head-to-head RCT Equivalence design	Open label pragmatic trial comparing technologies, choice of drug within a class left to local preference. Around 6% post-randomization exclusions, perhaps unusual in a pragmatic trial.	Identified features: • Patient heterogeneity • Blinding • No placebo (assay sensitivity?) • Poor compliance • Treatment crossovers	Intention to treat analysis with per-protocol as back up. Multiple imputation used for missing data. Study lacked power due to more variability in outcome than expected (more heterogeneous population, lower compliance, crossovers).